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EXPERIMENTAL OBSERVATIONS ON THE SURGICAL TREATMENT OF HYPERTENSION*†

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IN RECENT years surgical treatment of hypertension has come to the fore. This has consisted of denervation of some organs or section of nerves and excision of ganglia connected with the vasomotor apparatus of the abdomen. Denervation of the adrenals or kidneys, section of splanchnic nerves, section of anterior nerve roots, and excision of celiac or lumbar ganglia have been the operations of choice. Some of these procedures have been combined with unilateral or partial bilateral adrenalectomy. Irradiation of the adrenals by roentgen rays and partial adrenalectomy alone also have been tried. It is interesting to note that some of the methods which were regarded as effective at first were discarded later as useless even by the originators. It is also noteworthy that only the originators of each operation have been enthusiastic about the beneficial effects of their operation and have reported poor success or failure with other methods. As in the case of other methods of treatment, factors other than the level of the blood pressure, such as disappearance of headache, and other subjective symptoms have been used in the evaluation of the effect of the treatment. The unreliability of such criteria need not be stressed. It is a striking fact that no matter what the type of surgical operation on the nervous system, the percentage of cases in which a significant lowering of the blood pressure has been reported is about the same for all. After all the operations the percentage of cases in which there is a return of the blood pressure to normal is relatively small.

In evaluating the benefit of any surgical treatment, one must not forget the possible effect of the period of enforced rest which is involved in

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the operation and of the restriction of activity which follows. An explanation of the remainder of the beneficial effect in some cases is suggested by the investigations that have been made on the effect of the same operations on experimental hypertension due to renal ischemia. Briefly, this type of hypertension* can be produced at will by constricting both main renal arteries by means of a special clamp or by constricting the main artery of one kidney and at the same time, or later, removing the other kidney. It also can be accomplished by constricting the aorta above both renal arteries. If the constriction of the main renal arteries is moderate, but adequate, the blood pressure remains elevated, and there is little or no accompanying disturbance of renal function, although the hypertension persists for years. After several years of hypertension, the small arteries and arterioles show some thickening of the media and sometimes slight hyalinization of the intima, especially in retinal arterioles. This type is similar to the benign phase of human essential hypertension. If the constriction of the renal arteries is made severe, there follows hypertension and reduced renal function which may lead to fatal uremia. The arterioles of many organs show severe changes, such as hyalinization, fibrinoid degeneration, and necrosis. This type resembles the acute malignant phase of human essential hypertension. It is upon experience with the treatment of these two types of experimental hypertension that the comments on the surgical treatment of human hypertension are based. All of the operations on the nervous system that have been performed on man have also been carried out on animals without any effect in preventing or permanently lowering this type of experimental hypertension. In the animals more extensive operations have also been carried out. Total sympathectomy of thorax and abdomen and even pithing have had no effect on this type of experimental hypertension. The effect on the vasomotor apparatus is presumably the same as in man. There is, however, one notable difference between the two. In the animals the restriction of blood to the kidneys is effected by constriction of the main renal arteries by means of a rigid clamp. This is not altered by any of the operations on the nervous system. In man, on the contrary, the counterpart of the effect of the silver clamp is produced by the constriction or thickening of the wall of the arterioles of the kidney. It is conceivable, at least, that some of these vessels are merely in spasm and still under the influence of the nervous system and that they are, therefore, in a reversible state and can become dilated as a result of removal of the vasoconstrictor effect. The conclusion that follows from these experiments is that what improvement does occur from these operations, in all probability is, apart from the

*For complete bibliography, see Goldblatt, Harry: Experimental Hypertension Induced by Renal Ischemia, Harvey Lectures, Baltimore, 1937-38, Williams and Wilkins, Vol. 33.

effect of enforced rest, due to the improvement of the circulation through the kidneys and not to any effect on the rest of the vasomotor apparatus of the abdomen.

As concerns interference with the adrenals, one can merely state that the experimental work up to the present time shows that removal of the medulla of both adrenals has no significant effect in preventing or lowering blood pressure. This decreases materially the probability that epinephrine plays any part in the phenomenon. It has been found that experimental hypertension due to renal ischemia is not prevented or lowered by partial adrenalectomy, unless the amount of the cortex left is inadequate to support life. There is, therefore, no experimental basis for any surgical or other physical interference with the adrenals in the treatment of hypertension. It seems fair, in the circumstances, to sound a note of warning about this method of treatment which is still being practiced by some surgeons.

One obvious surgical therapeutic procedure which suggests itself as the result of this work is the possible improvement of blood supply to the functioning components of the kidney by increasing the collateral circulation. In the animals with experimental hypertension induced by renal ischemia, whenever there is a return of the blood pressure to a lower level, it is due to inadequate initial clamping of the renal arteries or to the development of effective accessory circulation by way of ureteral and capsular vessels, which may become very prominent. If, before constricting the renal artery, the kidney is decapsulated and adipose tissue or muscle is attached to the denuded cortical surface, the accessory circulation from the adherent tissues becomes very prominent and interferes with the development of pronounced elevation of blood pressure. Since, in the animals, the constriction is only of the main renal artery, such accessory circulation can be of functional significance. The fact that animals have survived several years the complete closure of both main renal arteries, when effected gradually, by increasing the constriction at intervals, is proof that such accessory circulation can be functionally highly effective. However, in human essential hypertension, the vascular disease most frequently involves also the afferent preglomerular arterioles, so that collateral communication with the larger vessels would not improve circulation to glomeruli. Whether improvement of blood supply to some glomeruli, to tubules and interstitial tissue would occur as a result of renal decapsulation and attachment of omentum, muscles, or other tissues to the surface of the kidney, and whether it would be effective in lowering blood pressure in human essential hypertension cannot be determined without trying this type of operation. Although I have hesitated to recommend it, yet there is probably more justification on an experimental basis for making this test than there has been for some of the surgical procedures that have already been practiced. The cases in which the surgical production of

accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone or their very large branches. The difficulty of making a diagnosis of this condition is obvious, so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis the procedure would be of greatly restricted value.

An interesting recent practical application of this work, which centers upon the renal origin of so-called essential hypertension, has been the finding in children and adults of hypertension associated with unilateral pyelonephritis and vascular disease, and the prompt return of the blood pressure to normal after excision of the diseased kidney. Until 1930, according to Bell and Pedersen, hypertension associated even with bilateral pyelonephritis had not been reported. Since then, Longcope and others have reported the occurrence of hypertension in some cases of bilateral pyelonephritis, and, from the meager studies of the kidneys, in these and in the cases of unilateral disease it has become probable that the hypertension associated with this condition in children and adults occurs only when there is associated vascular sclerosis or when the inflammatory disease produces the same effects on renal circulation as does vascular disease. In cases of unilateral arteriolar nephrosclerosis with hypertension, which have been reported by Moritz and Oldt, if the diagnosis could be made in life, removal of the diseased kidney might result in a return of the blood pressure to normal, as in the cases of unilateral pyelonephritis.* Unfortunately, unless the production of accessory circulation would be effective, nothing but transplantation of a normal kidney or kidneys, with the removal of both diseased kidneys, could be expected to relieve the hypertension associated with bilateral pyelonephritis or bilateral arteriolar sclerosis of the kidneys.

*From the James Buchanan Brady Urological Institute and Department of Medicine of Johns Hopkins Hospital, there have just been reported two cases of hypertension associated with unilateral renal vascular disease in which the removal of the diseased kidney resulted in a prompt return of the blood pressure to normal. A similar result has been obtained in a third unreported case (personal communication from Prof. Hugh Young).

SOME ASPECTS OF BLOOD PRESSURE REGULATION AND EXPERIMENTAL ARTERIAL HYPERTENSION*

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FOR many years physiologists have been occupied with the study of the mechanisms which regulate blood pressure. A precise and detailed knowledge of the physiologic regulation of endovascular pressure is the key, not only to the physiology of normal circulation, but perhaps also to the pathogenesis of chronic arterial hypertension.

It is known that the arterial pressure is largely controlled by the activity of the heart, the cardiac rate, the cardiac output, the circulating blood volume, and, mainly, by the peripheral vascular resistance, the vasomotor tone.

The arterial pressure is dependent upon factors which are essentially labile and variable. In spite of the numerous influences which, in an unbalanced physical system, would cause extreme variations in pressure, fluctuation of mean blood pressure under differing conditions is strikingly limited. In may be asked, therefore, what are the mechanisms which prevent such fluctuations and maintain and adjust the blood pressure in this precise and sensitive manner so as to control and regulate the circulation and nutrition of the cells, tissues, and organs of the body.

In recent years experimental investigations have demonstrated that the regulation of blood pressure is essentially and fundamentally an *automatic, proprioceptive reflex mechanism.* In fact, the endovascular pressure itself regulates automatically the cardiac output, the circulating blood volume, and the peripheral vascular resistance so well that the arterial pressure is maintained within or quickly restored to normal limits. This *homeostasis of the arterial pressure* is effected mainly by the intermediation of the pressoreceptor innervation of different arterial and venous vascular areas.

The early experiments of v. Cyon and Ludwig,[1] as well as the more recent researches of v. Anrep and Starling,[2] Ladon and myself[3-5] and De Burgh Daly and Verney[6] have shown that the cardioaortic vascular zone, especially the aortic arch, is provided with a pressoreceptive reflexogenic innervation (Fig. 1). When the endovascular pressure rises

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in the left heart or aortic arch, impulses ascend centripetally along the cardioaortic nerves, inducing reflex cardiac slowing, diminution of cardiac output, and peripheral vasodilatation. On the other hand, when this endovascular pressure falls, the same pressoreceptors induce reverse vasomotor and cardiac reactions, characterized by vasoconstriction, cardiac acceleration, and an increase of cardiac output. These reflexes tend to keep a balance between hypertension and hypotension and to maintain normal arterial pressure.

One knows further from the work of Cooper,[7] Marey,[8] Francois-Franck,[9] and Hedon[10] that variations of carotid-cephalic arterial pressure immediately produces cardiac and vasomotor reactions. Carotid-

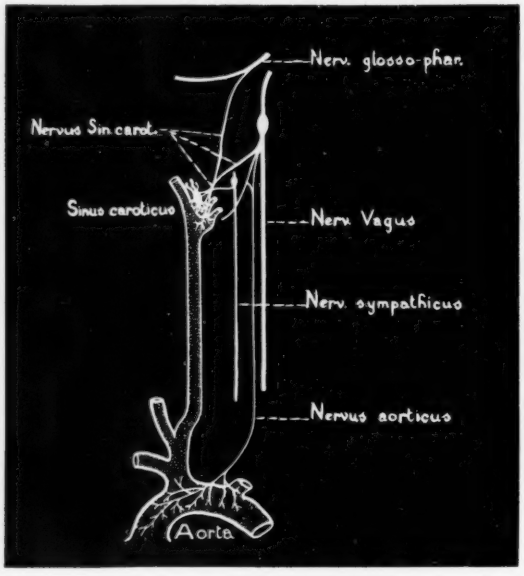

Fig. 1.—Diagram of the cardioaortic and carotid sinus pressosensitive innervation.

cephalic hypotension produced by clamping both carotid arteries induces acceleration of the heart, increase of cardiac output, and somatic vasoconstriction. The opposite phenomena, namely, cardiac slowing and somatic vasodilatation, are responses to carotid-cephalic hypertension. This mechanism of regulation of blood pressure was long attributed to the *direct* central influence of changes of blood pressure acting on the tonus of the cardiovascular centers.

The work of Czermack[11] and Concato[12] and the observations of Sollmann and Brown[13] showed, however, that the common carotid artery, particularly its bifurcation, may be the origin of cardiovascular reflexes elicited by mechanical manipulation, such as by compression of the neck in the region of the carotid bifurcation or by traction on the cephalic end of the carotid artery.

The experiments of Pagano[14] and Siciliano[15] in 1900 had already seriously damaged the concept of direct, central automatic regulation of blood pressure. But their experiments, which were incomplete and contradicted by Kaufmann,[16] passed almost unnoticed, and the classical theory of the direct central regulation of blood pressure was still accepted until 1924 when new investigations, performed mainly in the laboratory of Hering[17, 20] and in our laboratory,[4, 5] clarified the forgotten observations of Pagano and Siciliano and revealed the existence

Fig. 2.—Diagram of carotid sinus in man.

of the carotid sinus mechanism by which the carotid blood pressure controls reflexly the general arterial pressure.

The term "carotid sinus" signifies a specially innervated area of the bifurcation of the common carotid artery (Figs. 1 and 2). Within this area are the origins of the internal and external carotid and the occipital arteries, the carotid bulb (which is a bulbous dilatation at the root of the internal carotid), and the carotid body or carotid ganglion which lies between the bifurcating arteries. This region is connected with the central nervous system by means of a distinct group of nerve fibers constituting the carotid sinus nerves. The nerve fibers originate in the ad-

ventitial coat of the arteries of the carotid bifurcation, mainly in the carotid bulb, and in the endothelial lining of the vessels of the carotid ganglion, as shown chiefly by De Castro[18] and Nonidez.[19]

According to a technique (Fig. 3) developed in our laboratory, one or both carotid sinuses of a dog are isolated in situ from the circulation, taking care not to injure their innervation. Such isolated sinuses then are really segments of vessels with intact nerve supply and these segments may be perfused either by means of another dog or with a Dale-Schuster perfusing pump. In this manner the pressure within the lumen of this specialized and isolated segment of the vascular tree may be raised or lowered. Since this segment is connected to the animal only

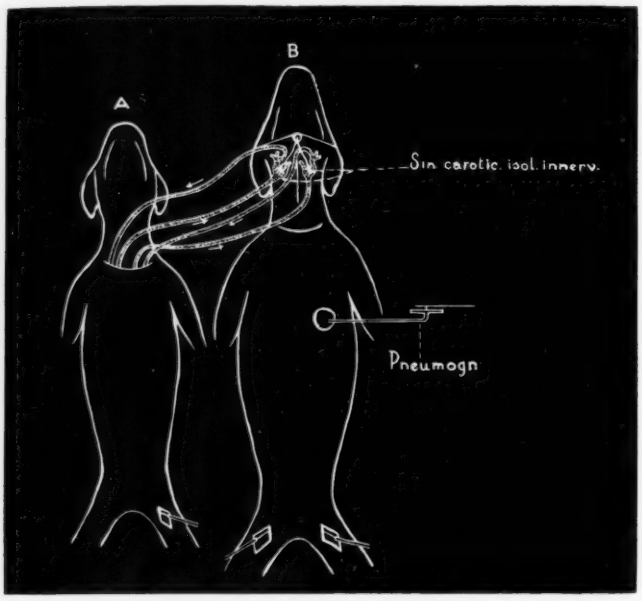

Fig. 3.—Technique of establishing isolated, innervated carotid sinuses in Dog B perfused by Dog A.

by intact nerves, it can be shown that it is only by reflexes originating within this area, due to differences in pressure, that the general blood pressure is regulated.

If the pressure inside the circulatory isolated but innervated carotid sinuses is increased, one observes (Fig. 4) that this rise of intracarotid sinus pressure is associated with a fall of the blood pressure in the general circulation of the dog. Together with the fall of arterial pressure, there is a slowing of the heart. Conversely, if the pressure is lowered in the isolated carotid sinus, the general blood pressure of the dog rises and the heart accelerates.

These experimental observations thus demonstrate that the general arterial blood pressure is automatically controlled by means of the endovascular pressure itself acting on the pressosensitive nerve endings of

the carotid sinuses. The pressosensitivity of the carotid sinus is very great; it has indeed been shown by Koch[20] and by my co-workers and myself[5] that, in the carotid sinus of the dog, an increase or a decrease of even 1 mm. mercury pressure from the normal arterial pressure is sufficient to produce reflex compensatory changes in the general blood pressure. Moreover, Bronk and Stella[21] could register action potential variations from the carotid sinus pressoreceptors with each systolic-diastolic variation of carotid sinus pressure.

Let us analyze briefly the components of these proprioceptive mechanisms of blood pressure regulation by the aortic and especially the carotid sinus pressoreceptor reflexes.

The regulation of the heart rate depends mainly upon reflex changes in the vagus tone and to a slight degree upon changes in the sympathetic activity.

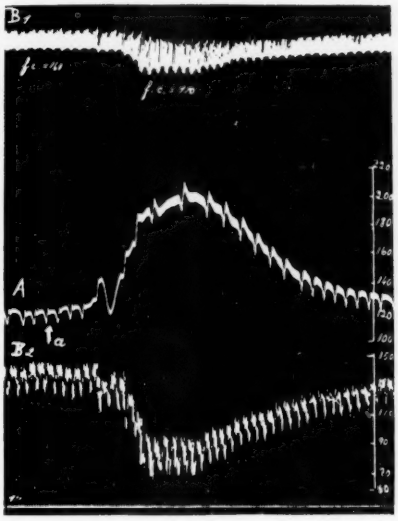

Fig. 4.—Dogs A and B prepared according to the technique shown in Fig. 3. Upper curve, heart rate of Dog B; middle curve, blood pressure of Dog A perfusing the carotid sinuses of Dog B; lower curve, femoral blood pressure of Dog B. At ↑*a*: adrenaline hypertension in Dog A, and hence in the carotid sinuses of Dog B, induces heart slowing and hypotension in Dog B.

The control of the circulating blood volume and the peripheral vascular resistance is mainly due to reflex changes in the arterial and venous tone and also to the changes in the tone of the arteriovenous anastomoses.

Thus, we find that an increase of carotid sinus pressure produces reflex arterial and venous dilatation and a reduction in caliber of the arteriovenous anastomoses. A lowered carotid sinus pressure produces, on the other hand, a reflex arteriolar and venous constriction and an opening of the arteriovenous anastomoses.

By means of various experimental methods, it has been shown[5] that these vascular reactions occur, to a certain extent, in the peripheral

vessels, but take place mostly in the splanchnic area; that is to say, the mesenteric vessels, the spleen, liver, intestines, and kidneys.

Concerning the reflex regulation of the venous vascular tone by the carotid sinus pressoreceptive reflexes, the investigations of Fleisch[22] and myself with Bouckaert, and Regniers[5] show that the mesenteric veins, isolated from general circulation but perfused in situ by means of Donegan's technique, contract reflexly in response to a lowering of carotid sinus pressure and dilate if the sinus pressure is increased. Thus, both the tone and the capacity of the abdominal venous reservoirs are controlled reflexly and automatically by the arterial blood pressure acting on the pressosensitive carotid sinus nerve endings.

The arteriolar and venous vascular tones are regulated not only by the carotid sinus and aortic reflexes by means of neurovascular influ-

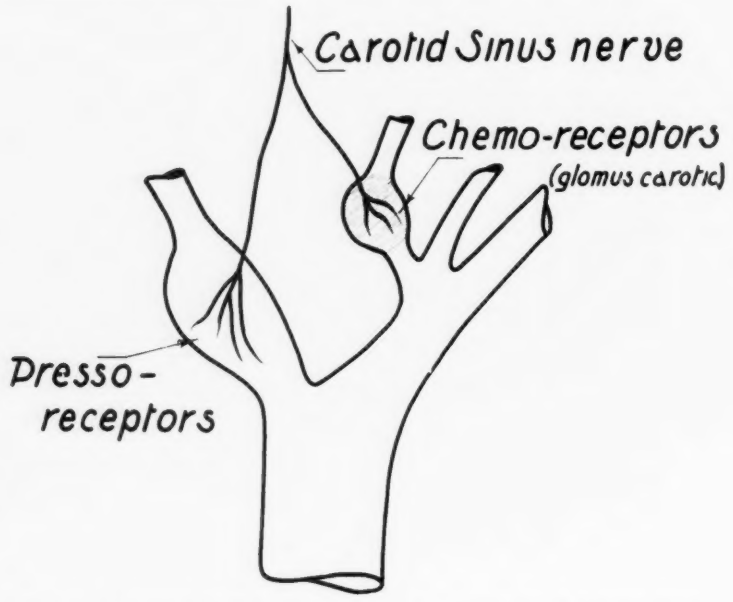

Fig. 5.—Diagram of the presso- and chemoreceptors of carotid sinus.

ences, but also by reflex alterations in the adrenaline output. Our experiments[4, 5] showed indeed that, when the pressure rises in the carotid sinus, the adrenaline discharge of the suprarenals is reflexly reduced; when the carotid sinus pressure is lowered, more adrenaline is liberated by the suprarenals.

Therefore, the arterial blood pressure, by acting on the pressoreceptors of the carotid sinus, provides one of the mechanisms for regulating the secretion and discharge of adrenaline, and thus further controls, in a humoral manner, the vascular tone, the heart rate, the circulatory blood volume, and probably also the caliber of the arteriovenous anastomoses.

I wish to point out that this suprarenal hormonal regulation of the circulation by the carotid sinus is only an accessory regulating mech-

anism. Indeed, experimental observations with Bouckaert and Nowak[23, 24] have shown that the reflex neurovascular regulation of the blood pressure occurs quite well in the absence of the suprarenal medullary secretion. The increased discharge of adrenaline in response to lowered carotid sinus pressure is thus comparable to the increased release of adrenaline in response to emergencies, as demonstrated by Cannon.[25]

Finally, another group of experiments has permitted us to assert that the carotid sinus zone, as well as the cardioaortic area, is provided with a reflexogenic innervation which is not only pressosensitive but also chemosensitive, so that changes in oxygen or carbon dioxide content in the blood and also the presence of several pharmacologic sub-

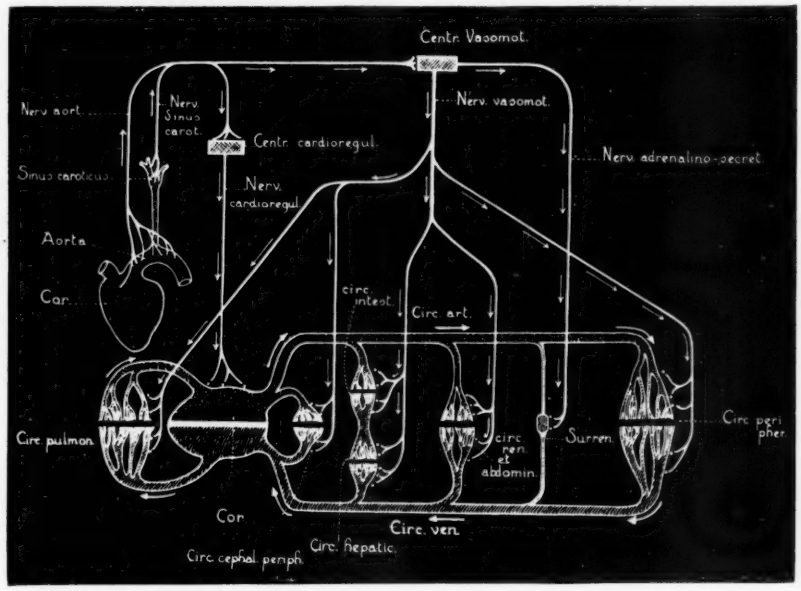

Fig. 6.—Diagram of the circulation and of the reflex neurovascular, neurocardiac, and adrenaline regulation of heart rate, vascular tone, and blood pressure by means of the cardioaortic and carotid sinus presso- and chemoreceptive mechanisms.

stances in the arterial blood can influence, by means of carotid sinus and aortic reflexes, the activity of the cardiovascular centers and thus modify the general blood pressure. These chemoreceptors of the carotid sinus are localized (Fig. 5) in the glomus caroticum, annexed to the carotid bifurcation, and are quite different from the pressoreceptors.

Fig. 6 shows schematically the afferent and efferent pathways of the proprioceptive mechanisms of cardiovascular regulation by means of the carotid sinus and cardioaortic presso- and chemosensitive areas.

Another question presents itself at this point: Are the cardioaortic and carotid sinus vascular zones the only regions provided with reflexogenic pressosensitivity and able to take part in the proprioceptive regution of heart rate, vascular tone, and blood pressure?

Experimental observations by Bainbridge[26] and by Mc Dowall[27] have shown that the right auricle, as well as the venae cavae at their entrance into the heart, are provided with receptors through which pressure changes in the venous system influence reflexly the heart rate and the arterial vascular tone.

More recently Schwiegk[28] showed that the branches of the pulmonary artery also are endowed with reflexogenic pressosensitivity regulating the heart rate and arterial vasomotor tone. Increase of pressure in the pulmonary arterial system causes reflex heart slowing and arterial vasodilatation, while lowering of pulmonary arterial pressure provokes the opposite cardiovascular reactions.

The centripetal pathways from these venoauricular and pulmonary arterial pressoreceptors are found in the cervical vagus nerves.

In 1929 we observed,[4] however, that experimental suppression of the cardioaortic, carotid sinus, and cervical vagus nerves did not abolish completely the proprioreceptive mechanism of cardiovascular regulation. Indeed, in a dog deprived of the pressosensitive reflexogenic innervation of the cardioaortic, carotid sinus, venoauricular, and pulmonary zones, the elevation of general arterial pressure still induced compensatory reactions characterized by vascular dilatation and diminution of adrenaline output. In the same animal arterial hypotension started the opposite compensatory reactions of vascular constriction and increased adrenaline secretion. This proprioceptive adaptation and control of vasomotor tone by the blood pressure is not of direct central origin. These reactions still persist in the "spinal" animal.

Experiments employing several different methods have permitted us, with the collaboration of Bouckaert, Farber, Hsu, and Wierzuchowski,[29, 30] to show that, in the dog deprived of carotid sinus, cardioaortic, pulmonary, and venous pressosensitive zones, as in the spinal animal, the proprioceptive regulation of vascular tone occurs through pressosensitive reflexes originating mostly from the vascular territory of the celiac and mesenteric arteries, and secondly from the territory of the thoracic arteries. These vasomotor reflex responses to blood pressure variations may arise in part from the mesenteric pressoreceptors located in the Pacinian mesenteric corpuscles, as shown by Gammon and Bronk,[31] who recently registered centripetal action currents, related to blood pressure changes, from these organs.

These experiments raise another question: Are all vessels provided with reflexogenic pressosensitivity? There are experimental facts which make it possible to answer in the negative. Proprioceptive regulation of general vascular tonus is effected through reflexes, the pressoreceptors of which are situated only in certain well-localized vascular areas; namely, the carotid sinus, cardioaortic, venoauricular, pulmonary arterial, and thoracicosplanchnic zones.

Fig. 7 shows schematically the main functions of the pressosensitive reflexogenic vascular areas in the proprioceptive cardiovascular regulation.

After this review of the proprioceptive mechanisms of the regulation of general blood pressure, I propose to examine the significance of these mechanisms in the pathology of chronic arterial hypertension.

The cardioaortic and carotid sinus nerves not only are the means of the automatic pressoreceptive reflex regulation of general arterial pressure but also are the *buffer or moderator nerves* of the blood pressure.[5, 17, 20] In fact, functional suppression of the aortic and carotid sinus nerves produces immediately an intense arterial hypertension; in dogs the pressure may rise from 130 to 250 to 300 as a consequence of the section of the aortic and carotid sinus nerves (Fig. 8 *I*). This marked increase of blood pressure is due to the release of vasoconstrictor and cardioaccelerator centers, the activity of which, under normal condi-

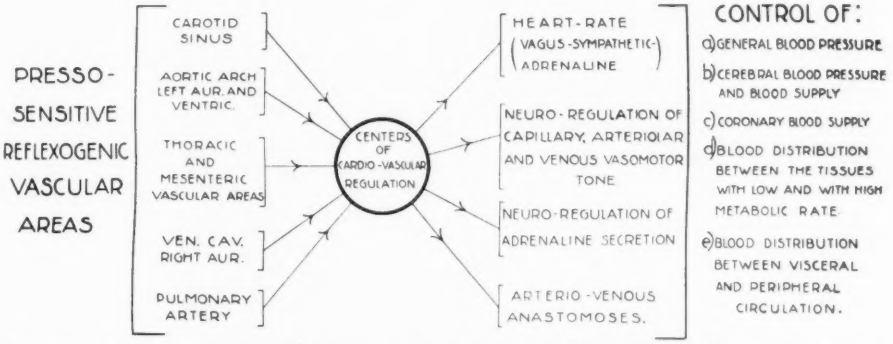
PRESSO-SENSITIVE REFLEXOGENIC VASCULAR AREAS
CAROTID SINUS
AORTIC ARCH LEFT AUR. AND VENTRIC.
THORACIC AND MESENTERIC VASCULAR AREAS
VEN. CAV. RIGHT AUR.
PULMONARY ARTERY
CENTERS OF CARDIO-VASCULAR REGULATION
HEART-RATE (VAGUS-SYMPATHETIC-ADRENALINE)
NEURO-REGULATION OF CAPILLARY, ARTERIOLAR AND VENOUS VASOMOTOR TONE
NEURO-REGULATION OF ADRENALINE SECRETION
ARTERIO-VENOUS ANASTOMOSES.
CONTROL OF:
a) GENERAL BLOOD PRESSURE
b) CEREBRAL BLOOD PRESSURE AND BLOOD SUPPLY
c) CORONARY BLOOD SUPPLY
d) BLOOD DISTRIBUTION BETWEEN THE TISSUES WITH LOW AND WITH HIGH METABOLIC RATE
e) BLOOD DISTRIBUTION BETWEEN VISCERAL AND PERIPHERAL CIRCULATION.

Fig. 7.—Diagram of the functions of the pressosensitive reflexogenic vascular areas in the proprioceptive cardiovascular regulation.

tions, is permanently moderated reflexly by the aortic and carotid sinus nerves. The moderator tone of these nerves is maintained and regulated by means of the pressure and the chemical constitution of the blood acting on the presso- and chemosensitive nerve endings of the cardioaortic and carotid sinus vascular areas.[5]

In dogs my co-workers and I[5, 32] have observed arterial hypertension maintained at 250 to 300 for periods of nine to twenty-six months after section of the cardioaortic and carotid sinus moderator nerves (Fig. 9). The same observation has been made by Nowak[33] on dogs up to three years after section of these moderator nerves. If, in a certain number of animals, section of the cardioaortic and carotid sinus nerves produces only a temporary hypertension, this is due to the presence of accessory fibers of the cardioaortic nerves in the vagus, or because in certain animals the pulmonary and mesenteric intestinal pressosensitive nerves may take over the moderator function of the cardioaortic and carotid sinus nerves.

The degree of hypertension which develops after section of the moderator nerves depends mainly upon the sympathetic vasopressor tonus. This tonus is an index of the state of activity in the cortical psychomotor, hypothalamic, and bulbar centers, as well as the result of a series of humoral and cellular factors among which are the blood supply to the sympathetic centers and the CO_2 and oxygen content of the blood.

With Bacq, Brouha, and Bouckaert, I[32, 34] could show, indeed, the role of the vasopressor sympathetics in the mechanism of experimental hypertension produced by exclusion of the moderator nerves.

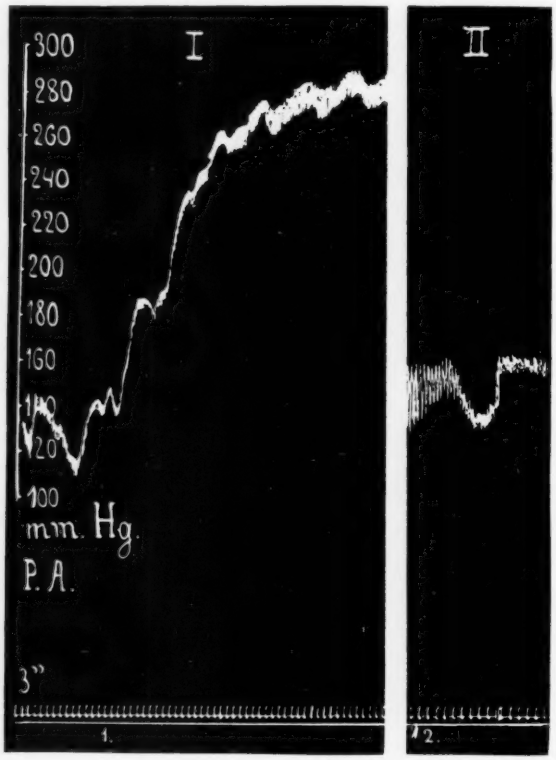

Fig. 8.—*I*, blood pressure of a normal dog; at *1*, section of the four moderator nerves; hypertension. *II*, blood pressure of a totally sympathectomized dog; at *2*, section of the four moderator nerves; no hypertension.

In dogs total excision of the sympathetic paravertebral ganglionic chains, from the stellate ganglia down to the pelvic ganglion, performed in three operative stages, prevents (Fig. 8 *II*) or causes the disappearance of this type of experimental hypertension. We noticed also that the pressoreceptive reflexes of cardioaortic and carotid sinus origin, regulating vascular tone and arterial pressure, are absent in the totally sympathectomized dog. No vasomotor response could be detected either by reflex or direct stimulation of the vasomotor centers in dogs up to several months and for as long as one year after total removal of the sympathetic chains. The general arterial pressure (Fig. 8 *II*), the ther-

moregulation, the psychic and motor behavior of these totally sympathectomized dogs were, however, normal as also shown by Samaan,[35] Brouha, Cannon, and Dill.[36] After each operative stage of the sympathectomy, the animal passes, of course, through a period of one or two weeks of general depression; the blood pressure is lowered as a consequence of the removal of an important part of the vasomotor tone of central origin. Soon, a progressive rise in peripheral vascular resistance is restored by means of a vasopressor mechanism, originating, in part, in the sympathetic synapses located more peripheral to the paravertebral chains, and in the vascular wall. Thus the general blood pressure returns to normal levels. At complete rest, the blood pressure of the totally sympathectomized dog, however, may be somewhat under the mean level of normal dogs as a consequence of the slow rate of the heart deprived of its sympathetic innervation and controlled only by the vagal cardioinhibitory tone.

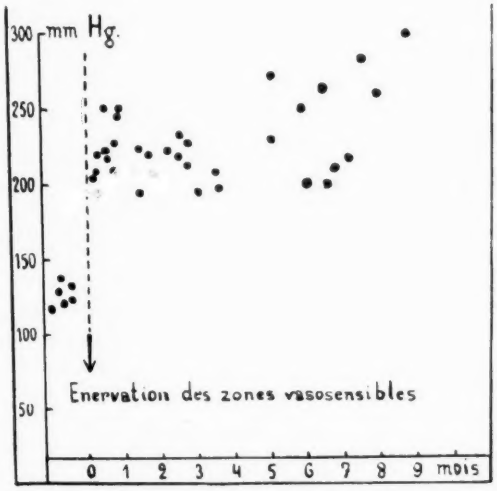

Fig. 9.—Blood pressure of six dogs before and after section of the four moderator nerves.

The question arises: Is the experimental hypertension induced by exclusion of the moderator nerves related to permanent clinical hypertension? We can, at least, answer a part of this question in the negative. This form of experimental hypertension varies from the typical nephropathic variety, but resembles more closely the so-called "essential neurogenic hypertension." This suggests that a functional deficiency of the moderator nerves, either in the region of the vasoconstrictor centers, in the region of the peripheral pressoreceptors, or in the region of the peripheral vasoconstrictor nerves, could be the underlying cause for essential hypertension and that surgical interruption of the efferent vasopressor sympathetic nerve paths might be indicated in this condition of "neurogenic" hypertension.

Recently, Allen and Adson[37] concluded from their clinical observations that bilateral resection of the splanchnic nerves, celiac ganglion, and two upper lumbar sympathetic ganglions, for essential hypertension, can be carried out without undue risk, that patients are not disabled as a result of this operation, and that the blood pressure of many of them is significantly reduced. Other patients note amelioration or relief of symptoms even when their blood pressures have not been significantly reduced.

A second method which will produce experimental hypertension was described by Dixon and Heller.[38] These authors injected a kaolin suspension into the cerebral ventricles or into the subarachnoid space. The mechanical compression, produced by the kaolin, led to cerebral anoxemia which particularly sensitizes the vasopressor centers to the stimulating action of CO_2. That anemia and anoxemia may stimulate the vasopressor centers has been demonstrated by several experimenters. Raab[39] has shown, in the laboratory of Cannon, that central anemia, especially central acidosis, stimulates the vasopressor centers and increases their sensitivity to the humoral CO_2. In our laboratory, Nowak and Samaan,[40] by perfusing the isolated head connected to the trunk only by the spinal vasomotor pathways, also produced evidence that acute anemia alone in the cerebral circulation provokes an intense somatic arterial hypertension. Experiments of Nowak[41] further observed that the permanent decrease of cerebral blood supply by ligature of the carotid arteries, vertebral and spinal arteries may induce, in dogs, a condition of permanent arterial hypertension. These experimental observations support the views of Kylin[42] and Raab,[43] who believe that some forms of clinical hypertension are related to some process of anoxic nature, such as endarteritis, localized in the region of the vasopressor centers.

Recently Goldblatt and co-workers[44] made a very important observation. They showed that, in the dog and in the monkey, renal ischemia by permanent incomplete compression of the renal arteries caused chronic, progressive arterial hypertension, with elevation of both the systolic and the diastolic pressures. This fact has largely been confirmed by Page[45] and others and in our laboratory by Elaut,[46] Bouckaert, and myself.[47] In our experiments we obtained permanent hypertension in dogs reaching 245. Furthermore, we observed[47] that the carotid sinus vasopressor and hypertensive reflexes were especially active in such hypertensive dogs. Page[45] and Collins[48] observed that in dogs excision of the extrinsic renal nerves alone does not prevent experimental hypertension due to renal ischemia. The experiments of Goldblatt and his collaborators[49] showed that neither excision of one suprarenal body with denervation and destruction of the medulla of the other suprarenal, nor excision of the splanchnic nerves and the lower dorsal ganglia, which constitute an

important part of the sympathetic vasopressor system, prevents or cures experimental hypertension produced by renal ischemia.

More recently experiments performed by Bayless, Bouckaert, Elaut, and Samaan, and myself,[50] showed that complete excision of the whole sympathetic ganglionic chains in dogs also does not prevent the arterial hypertension following renal ischemia. The same observations have been made by Freeman and Page,[51] and Alpert, Alving, and Grimson.[52]

Our experiments[47, 50] suggest that the arterial hypertension induced by renal ischemia may be due to an humoral factor which increases the excitability of the peripheral blood vessels to constrictor stimulations, mainly to the neurogenic vasoconstrictor influences; the same humoral factor inducing, on the other hand, a direct peripheral vasoconstriction and a disturbance in the physiologic mechanisms of the pressoreceptive reflex regulation of blood pressure. The sympathectomy up to the total removal of both ganglionic chains neither prevents nor cures this experi-

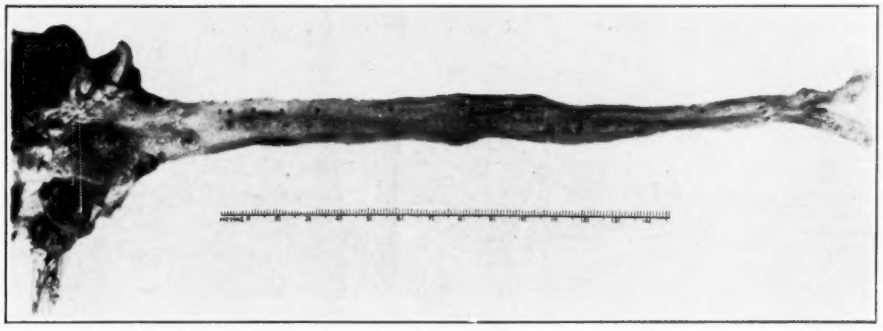

Fig. 10.—Lesions in the aorta of a thyroidectomized dog treated with large doses of vitamin D_2.

mental nephrogenic hypertension. But, as pointed out by Goldblatt, although the results of these investigations are in agreement with the conclusions of Prinzmetal and Wilson[53] and of Pickering[54] concerning the part played by the vasomotor system in human hypertension of nephropathic origin, yet they do not necessarily exclude some beneficial effects of operations on the vasomotor system or on the suprarenal glands in some cases of nephropathic hypertension. But we agree that further experimental and clinical studies are necessary to evaluate adequately the indications and the results of these surgical interventions.

A fourth method of producing experimental arterial hypertension is that indicated by Appelrot.[55] Further researches along this line were carried out by Handovsky[56] in this laboratory with the collaboration of Goormaghtigh,[56] of the Department of Pathology.

Their studies show that the repeated administration of relatively large doses of vitamin D_2 (calciferol) to dogs provoked a progressive augmentation of the arterial blood pressure. It was noticed also that the experimental dogs were very sensitive to the hypertensive action of adrenaline.

In the kidneys and elsewhere certain vascular lesions, mainly arteriolonecrosis, developed which could be almost superimposed upon those found in human eclampsia, diphtheria, and scarlet fever. It is furthermore interesting to mention that vitamin D_2, which provokes arteriosclerosis in the rat and rabbit, does not induce the same vascular changes in the dog, unless one deprives this animal of its thyroid gland. Thus, in the thyroidectomized dog the administration of vitamin D_2 provokes arterial hypertension and with it intense and unusual vascular changes in the aorta and its major branches (Fig. 10), and typical lesions in the smaller arteries. We believe that these observations are interesting, since this form of experimental hypertension, characterized by high pressure and vascular lesions and sclerosis, resembles some types of human hypertension. As a matter of fact, many pathologists (Rössle,[57] Wegelin,[58] Behr,[59] Schmidtmann[60]) and clinicians have referred to a relationship between the thyroid gland, arteriosclerosis, and hypertension. The researches of Aub and his collaborators[61] showed especially the close relationship between the thyroid and calcium metabolism.

These different groups of investigations surveyed in this lecture show once more the bonds closely uniting experimental physiology, pathology, and surgery in attempts to elucidate the mechanisms regulating arterial blood pressure and the causes of hypertension. The knowledge thus gained, it is hoped, will lead to a more adequate treatment of this very important disease.

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ESSENTIAL HYPERTENSION: THE SELECTION OF CASES AND RESULTS OBTAINED BY SUBDIAPHRAGMATIC EXTENSIVE SYMPATHECTOMY*

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HYPERTENSION, or persistent elevation of the blood pressure, may produce progressively severe symptoms and in spite of all types of treatment it may terminate fatally. In addition to the medical measures used in treating the more serious types of hypertension, operations upon the sympathetic nervous system have been devised and carried out in a large number of cases; the mortality has been low and the results have been gratifying. However, at the Mayo Clinic we have been impressed with the importance of the selection of cases suitable for operation. Subdiaphragmatic extensive sympathectomy has been performed in 158 cases in the Section on Neurosurgery at the Mayo Clinic. There has not been an operative death and there were only five deaths after operation. Following the operation, the clinical improvement varied with the progress of the disease, the age of the patient, and the amount of vascular, cardiac, and renal damage. To determine the amount of potential physiologic response obtainable following sympathetic denervation, certain tests have been devised (Table I). These tests have prevented unsuccessful operations and have indicated in which cases a satisfactory lowering of the blood pressure or relief of clinical symptoms may be expected to occur after the operation.

Table I

Preoperative Tests for Hypertension

1. Effect of rest and sleep for 24 hours
2. Effect of 3 gr. sodium amytal each hour for 3 doses
3. Effect of ½ gr. sodium nitrite each hour for 6 doses
4. Effect of 5% pentothal sodium intravenously

In essential hypertension there is increased peripheral arterial resistance, which is attributable to abnormal response of the arterioles to certain stimuli that produce marked fluctuation in blood pressure, emotion or cold increasing it greatly. There is some evidence that there are no abnormal vasomotor stimuli in essential hypertension; hence, it must be assumed that the arterioles react excessively to normal vasomotor stimuli.

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Postoperative observations have shown that, when the blood pressure fluctuates widely and reaches low levels at times, operation (that is, interruption of vasomotor impulses) is most beneficial, but, when the blood pressure is fixed at high levels, surgical treatment is ordinarily of little value. This emphasizes the necessity of preoperative tests to determine the flexibility of the blood pressure.

For convenience, essential hypertension has been divided into four clinical groups: Group 1 consists of cases in which there are mild sclerosis of the retinal arteries and a slight increase in blood pressure, which ordinarily becomes normal as a result of rest. In Group 2 have been placed cases in which there are moderate to severe hypertension, moderate sclerosis of the retinal arteries, and occasionally venous thrombosis and arteriosclerotic retinitis. Group 3 includes cases in which there is moderate to severe hypertension associated with a definite angiospastic retinitis. The severe and advanced types of the disease are included in Group 4; in the cases in this group there is very severe hypertension that is associated with an angiospastic retinitis and edema of the optic disks. This classification may be unsatisfactory because it fails to indicate the importance of the rapidity of progression. As a working basis, however, the classification is acceptable, since the seriousness of hypertension ordinarily increases progressively as the number of the group into which it is classified increases.

The medical treatment of mild essential hypertension is usually satisfactory but severe hypertension does not respond satisfactorily to medicine and diet. Some patients who have moderate hypertension Group 2 or 3 respond rather well to medical treatment; however, a nontoxic, adequate and prolonged vasodilator would solve the problem of the treatment in many cases. Unfortunately, no such substance is available. The nitrites, acetylcholine and acetyl-beta-methylcholine have in common a vasodilating action which is too short to be very valuable. Bismuth subnitrate, when administered orally, is of little value. There is some evidence that potassium thiocyanate may be effective (both before and after operation), but the dosage must be carefully regulated. The sedatives, particularly the barbiturates, are the most valuable drugs. The amount of sedative drug which should be given three or four times a day should be great enough to abolish nervousness and restlessness and small enough to avoid drowsiness and excessively slowed mental reactions. Many patients suffering from essential hypertension do not respond adequately to medical treatment. Surgical treatment is being advised only in these cases.

The purpose of surgical treatment of essential hypertension is to produce prolonged vasodilatation by interrupting the vasoconstrictor nerves to certain parts of the arterial system. Among the earliest operations employed were bilateral lumbar sympathetic ganglionectomy and cervicothoracic sympathetic ganglionectomy. These procedures were

not effective in lowering the blood pressure for a prolonged period because the operation was limited in its scope in that it did not denervate a sufficient vascular area. A more extensive operation consisting of intradural section of the ventral roots of the spinal nerves from the sixth thoracic segment to the second lumbar segment interrupts the sympathetic fibers which pass through these roots and which carry vasoconstrictor impulses. The entire vascular area below the diaphragm is thus denervated; this creates a reservoir which is unaffected when the undenervated vessels go into a spasm. Also, the suprarenal glands are denervated by interrupting the sympathetic fibers before they enter the capsules of the glands. This eliminates the central influence in producing excessive secretion of epinephrine under emotional stress. A thorough denervation of renal arteries and arterioles is performed. This increases the circulation of the kidneys and aids in the elimination of metabolic products which may play some role in the production of hypertension.

Following rhizotomy, the values for both the systolic and diastolic blood pressures of some patients remained lower than they were before the operation. This relieved the symptoms of hypertension. However, laminectomy and rhizotomy involved an unwarrantable surgical risk and the section of the splanchnic nerves alone proved inadequate in relieving hypertension. Therefore, the resection of all three splanchnic nerves, with a portion of the celiac ganglion, and removal of the upper lumbar ganglions on each side through a subdiaphragmatic approach was finally adopted (Fig. 1). In a rather large series of cases resection of one-third to one-half of each suprarenal gland was done, but this procedure has been discontinued; however, the glands are palpated for the presence of a tumor. The operation is divided into two stages and an interval of ten days is allowed to elapse between the operations on the right and the left sides respectively. From our studies, the subdiaphragmatic extensive sympathectomy is larger in scope and interrupts more thoroughly the efferent fibers from the thoracolumbar sympathetic outflow than does the supradiaphragmatic operation.

The futility of carrying out extensive sympathectomy in cases of hypertension in which there is irreparable damage to the cardiovascular mechanism is apparent. The operation should not be considered in a case in which there is mild and slowly progressive disease that is amenable to medical treatment. Operation seems most efficacious in the definite vasospastic type of hypertension in which sharp and brisk rises in blood pressure occur when the hands are immersed in cold water and in cases in which a marked fall in blood pressure is produced when pentothal sodium, sodium amytal, or a nitrite is administered. As an average rule, the patient must be under 50 years of age and the hypertension must be classed as of Group 2 or 3.

The so-called cold test is carried out by determining the blood pressure while the patient is resting and by continuing the determination until the value for the blood pressure reaches a basal level. A hand is then immersed, to the wrist, in water at 4° C. for one minute, and the blood pressure is determined at the end of thirty seconds and of one minute

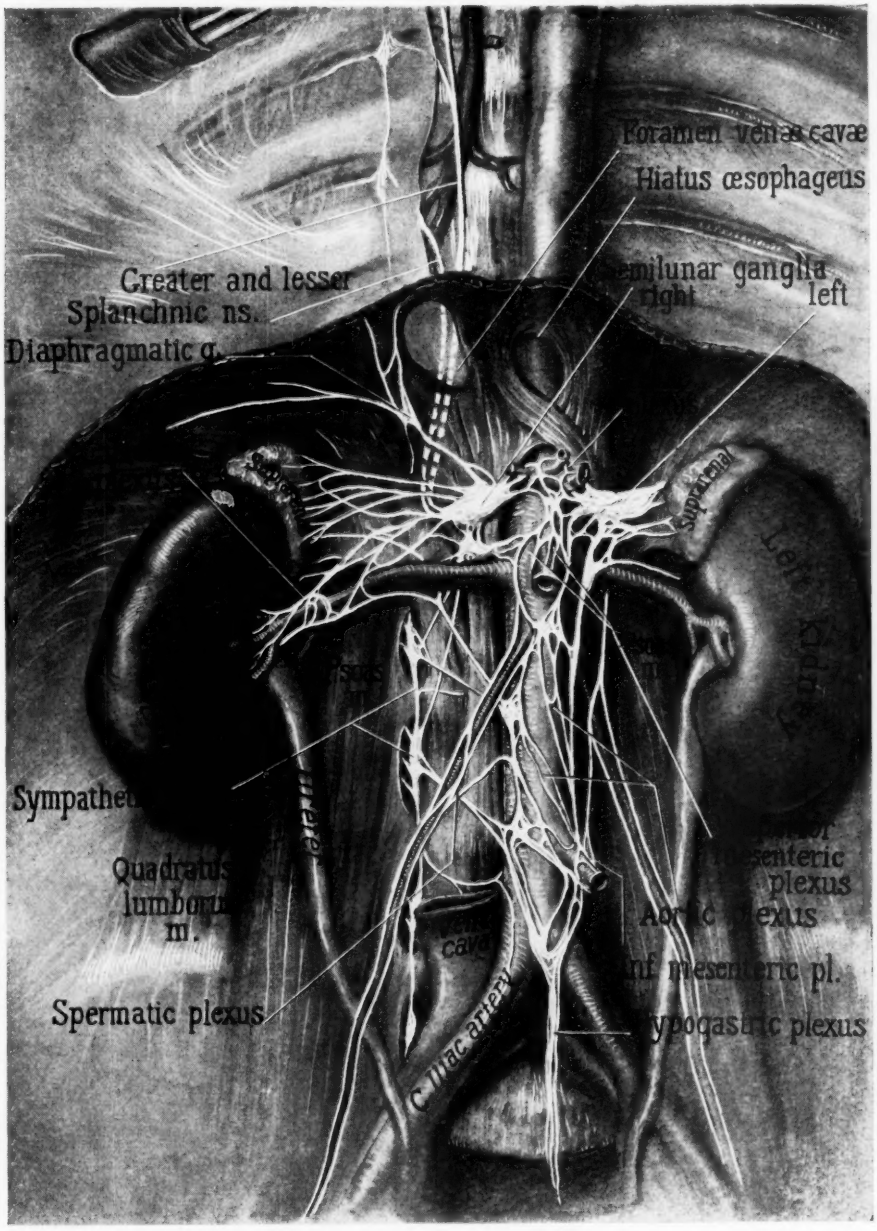

Fig. 1.—Anatomic representation of the major, minor, and lesser splanchnic nerves, celiac ganglion, upper lumbar sympathetic ganglions, and interruption of the sympathetic fibers in subdiaphragmatic extensive sympathectomy (From Labat: *Regional Anesthesia*, W. B. Saunders Company).

thereafter. The highest value is considered characteristic of the response. The response of the blood pressure to this test is a measure of the way in which it responds on innumerable occasions to such stimuli as anxiety, fright, and mental stress and strain. In cases in which operation has produced a significant decrease in blood pressure, the systolic blood pressure responds less sharply to the test than does the diastolic pressure.

The following standard tests have been adopted and operation is advised only for patients whose blood pressure responds satisfactorily preoperatively: (1) slow and intermittent intravenous injection of a 5 per cent solution of pentothal until there is no further drop in the blood pressure; ordinarily 500 mg. to 1 gm. of the drug is injected; (2) administration of 3 gr. (0.2 gm.) of sodium amytal each hour for three successive hours; (3) administration of ½ gr. (0.032 gm.) of sodium nitrite at intervals of thirty minutes until six doses have been given, and (4) hourly determination of blood pressure during rest and sleep for a minimum of twenty-four consecutive hours.

If the blood pressure decreases to normal or to nearly normal as a result of all these measures, the patient may be considered a satisfactory candidate for operation. If the response of the blood pressure to these measures is inadequate, the effect of operation is almost certain to be unsatisfactory. Unfortunately, even when these tests indicate that results of operation should be satisfactory, the actual results obtained will not necessarily be as good as the tests indicate. In other words, in spite of satisfactory response of the blood pressure to tests before operation it is possible that the blood pressure will not be reduced significantly by operation. At the clinic, we have made it a practice to perform the operation only in cases in which hypertension has been progressive in spite of medical supervision. However, we wish to emphasize that in almost every case of essential hypertension there is a period during which operation may be a valuable therapeutic procedure and one during which operation will almost certainly be valueless. Hence, if patients who have essential hypertension are to be operated upon, operation must be performed before the blood pressure becomes relatively fixed at high levels.

Contraindications for operation are as follows: An age of more than 50 years, congestive heart failure, angina pectoris, marked renal insufficiency, and advanced arteriosclerosis. Spasm and apparent sclerosis of the retinal arteries, retinitis, moderate enlargement of the heart, inversion of T-waves in the electrocardiogram, albuminuria, slight reduction in renal function, and a cerebrovascular accident from which recovery has been satisfactory are not in themselves considered contraindications to operation.

In carrying out extensive sympathectomy, the incision employed and the position of the patient on the operating table are similar to those employed for exploration of the kidney, except that the upper portion of the incision is extended high enough to include the oblique fibers of the latissimus dorsi muscle which will expose the twelfth rib. The incision is extended downward and outward over Petit's triangle, in order to expose the capsule of the perinephritic fat. Periosteal resection of the twelfth rib is then done; care is taken not to injure the pleura. The subcostal ligament of the twelfth rib is then incised; this allows upward retraction of the intercostal vessels and nerves and affords adequate exposure of the splanchnic nerves and lumbar ganglions. The liver is displaced forward and downward, as well as the capsule of perinephritic

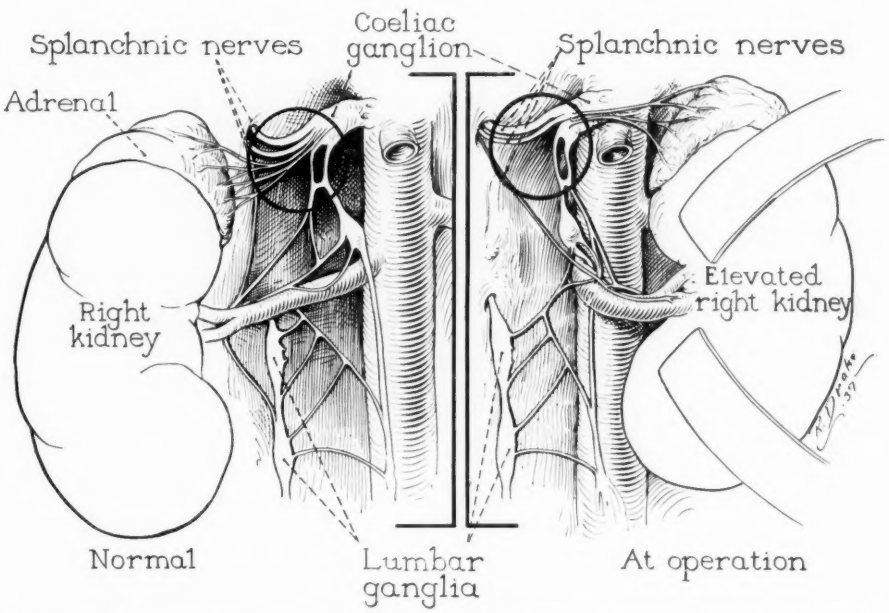

Fig. 2.—Diagrammatic representation of subdiaphragmatic sympathectomy, showing the normal relation of the ganglions and rami (the kidney has been retracted).

fat. At this point a laparotomy sponge that has been moistened in physiologic saline solution is inserted to protect the peritoneum and its contents, which are being dissected from the underlying muscles. Gentle dissection with moist cotton-ball sponges reveals first a splanchnic trunk which is composed of major, minor, and lesser splanchnic nerves, which are descending from above downward between the two crura of the diaphragm. They are about 2 cm. in length and end in the celiac ganglions. The resection includes the greater portion of the ganglion and the splanchnic nerves. The first and second lumbar sympathetic ganglions are exposed along the mesial border of the psoas muscle, and they are removed with the intervening trunk in order to interrupt fibers that pass downward in the lower end of the sympathetic trunk as well

as to interrupt white rami carrying efferent impulses to the upper two sympathetic lumbar ganglions. In this manner the splanchnic vessels, the suprarenal glands, and the kidneys are denervated (Fig. 2). The muscular fascial planes are approximated with continuous and interrupted sutures of chromic catgut and the skin is closed with silk sutures.

Following splanchnic resection and removal of the lumbar ganglions, the sweating function of the feet and lower part of the legs is lost. The cutaneous temperature is definitely increased and continues to remain so permanently. There is paralysis of the ejaculatory powers and of the muscles of the urogenital trigon that is similar to that which follows neurectomy of the presacral nerves. The menstrual cycle is not altered; moreover, the reproductive functions of the female are not changed. However, sterility of the male does result, although potentia and libido fortunately are not disturbed. Although this extensive sympathectomy deprives the small and large intestine, the ureters, and the bladder of the sympathetic innervation, it does not appear to increase the frequency or urgency of micturition or of defecation. Curiously enough, the atonic intestine, the dilated colon which so frequently troubles constipated people, and Hirschsprung's disease are definitely improved by this operation, since section of the sympathetic fibers to the intestine results in decrease of the inhibitory stimuli. The same applies to the muscular mechanism of the ureters and bladder.

Two definite phenomena in the cardiovascular mechanism develop following this operation. The first is a fall in blood pressure which occurs when patients first get out of bed and stand in the erect position. The second is the development of tachycardia. The first can be relieved with a tight binder and the second can be overcome by a decrease in exertion.

The effect of operation on symptoms, while variable, is roughly proportional to the effect on the blood pressure. However, patients not infrequently note relief of headache, fatigue, pain in the thorax, "dizziness," and nervousness, in spite of the fact that the blood pressure has not been greatly reduced by operation. It is probable that some of the symptoms associated with hypertension, such as headache, may occur only when the value for the blood pressure reaches an excessively high level. Operation which may reduce blood pressure only slightly may lower it sufficiently to prevent the occurrence of some of the symptoms. In most instances in which the blood pressure has been greatly reduced by operation, headache is relieved, pain in the thorax disappears, fatigue is lessened, and the patients gain weight and generally feel greatly improved. Many of them note diminution of nervousness and of a "let down" feeling, which gratifies them. Some patients have said that they feel "entirely well" or "better than in several years." In general, about 70 per cent of the entire group of patients were benefited clinically.

Some patients whose blood pressure has been greatly reduced by operation continue to note undue fatigue, weakness, and dyspnea for weeks or months after operation. One patient whose condition was followed closely did not regain normal strength until about six months after operation. We have not been able to determine definitely that the patients who noticed these symptoms following operation are those who continue to have orthostatic hypotension, but it appears that this is so.

SUMMARY

The surgical treatment of hypertension, which consists of subdiaphragmatic resection of the major, minor, and lesser splanchnic nerves, celiac ganglion, and lumbar sympathetic ganglions, is associated with a small risk and is followed by satisfactory alleviation of symptoms in selected cases.

Assuming that all hypertension can be divided into four groups, depending upon the severity, Group 1 does not require surgical treatment and Group 4 is too severe and too far advanced to warrant the expectation of adequate results. Groups 2 and 3 then should be considered for operative treatment. More important than the group are the preoperative tests which indicate the potential physiologic changes that will follow sympathetic denervation of the vascular area below the diaphragm.

The so-called cold test indicates the upper limits of the blood pressure resulting from emotion or cold. The four other tests indicate the lower limits of the blood pressure readings associated with prolonged vasodilatation, and, therefore, denote the probable values for the blood pressure following extensive sympathectomy. They are as follows: (1) Twenty-four consecutive hourly determinations of the blood pressure are made while the patient is in bed, to establish the maximal blood pressure, the minimal blood pressure, and the mean or average blood pressure. (2) Slow and intermittent intravenous injection of a 5 per cent solution of pentothal sodium is made until there is no further drop in blood pressure. (3) One-half grain (0.032 gm.) of sodium nitrite is administered at intervals of thirty minutes until six doses have been given. (4) Hourly determinations of blood pressure are made during rest and sleep for a minimum of twenty-four hours.

If the blood pressure drops to nearly normal and if the patient is less than 50 years of age, the operation should be considered.

The results in a large series of cases have been quite satisfactory. The effect of the operation is physiologic in character, and, if so considered, the results justify the procedure.

BLOOD POTASSIUM DURING EXPERIMENTAL SHOCK*

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IN MAMMALS the extracellular body fluids contain from 13 to 25 mg. potassium per 100 c.c. and in individuals under basal conditions the level in the plasma remains remarkably constant, although the basic levels for individuals of the same species may differ as much as 20 per cent. It is well known that living cells, both plant and animal, contain from seven to twenty-five times as much potassium as their surrounding media.

With manifold K differences outside and inside the cell, it seemed reasonable to postulate that experimental procedures resulting in extensive tissue destruction, trauma, or injury causing increased cell permeability should result in increased extracellular potassium. Increases in the blood would only be expected to occur if the K was released from the cells too rapidly for the potassium regulating mechanism to handle. If the extracellular body fluids are depleted, their replacement by highly potassic cellular fluids should also result in a potassium rise.

It should be noted that even with the injections of potassium salts the plasma K level cannot be altered for long in normal animals (Zwemer and Truszkowski, 1937; Truszkowski and Zwemer, 1938), and that prolonged hyperpotassemia can only be produced by repeated injections. Marked elevations are injurious to the body regardless of whether the rise is a result of potassium injected, ingested, or released from the animal's own cells (Webster and Brennan, 1927). In the present paper we have followed the blood potassium levels after extensive cell injury or fluid depletion through shock to death.

EXPERIMENTAL PROCEDURES

Cats were used in the experiments and unless otherwise noted peripheral ear blood samples were taken for whole blood potassium analysis by the method of Truszkowski and Zwemer (1937). The red blood cells of the cat have a low potassium content and whole blood of this species is therefore a valid indicator of K changes. Parallel serum values are given in the hemorrhage experiments, in which extensive

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blood sampling would not complicate the picture. Ether anesthesia was used during the period of operative and traumatic procedures in the acute experiments, with the exception of the cases in which sodium amytal was used. Blood density was determined by the method of Barbour and Hamilton (1926). A condition of primary shock was produced within a few hours by hemorrhage, crushing of limbs, or manipulation of viscera. Slower development of the secondary shock syndrome occurred after intestinal obstruction, enterostomy, and pancreatitis.

RESULTS

Our impression based on thousands of potassium determinations in a number of animals species and man is that plasma potassium is remarkably constant and difficult to alter for long. The relative constancy of plasma potassium is shown in an animal in which only a small amount of tissue was damaged with no production of pain. The blood potassium was followed for a period of days, with frequent samples taken on the first day (Protocol 1).

Analysis of blood samples from an animal which remained under amytal anesthesia for thirty hours during which time eight samples of blood were taken (Protocol 2) showed no change in potassium. Under amytal the variations were less than 2 mg. per cent in either direction from the initial value. Initially and when the animal recovered, the values were somewhat higher.

In the hemorrhage experiments the values also varied little until the amount of blood removed was a large proportion of the initial estimated total.

Although one might expect that crushing of muscle and hemorrhage would be the procedures most likely to raise the plasma potassium content from endogenous sources, these animals showed K rises terminally only. This agrees with Stewart (1936) who found no plasma K rise with hemorrhage, but a marked K diuresis. He did not bleed his dogs to death. Kerr (1926) and Thaler (1935) report plasma K increase after hemorrhage. It was easier to produce shock by visceral manipulation than by trauma to the extremities and concomitantly the viscera lose their K content much more easily.

The results in individual animals are illustrated by complete protocols of the effects of fatal hemorrhage, limb trauma, and visceral manipulation as listed in Table I. Some were graphed, with information supplementary to the K determination.

Table II gives data from sixteen animals in which a condition of secondary shock occurred. The initial blood potassium, the blood potassium during shock, and the interval between these two determina-

tions are given. The number of blood samples analyzed for their potassium content and the procedure initiating the shock syndrome are given also.

In animals acutely shocked with potassium salts, the blood K rises and the onset of symptoms are abrupt as in the present acute experiments (Table I); whereas, with the prolonged moderately elevated rises obtained with repeated injections (Truszkowski and Zwemer, 1938), the symptoms resemble those of the second group of cases (Table II).

The source of the blood sample is important, as it has been found in other experiments (Zwemer and Pike, 1938) that venous bloods coming from different organs may vary markedly in their potassium content. This finding and more specific studies of nerve excitation and of anesthetics on potassium changes in shock will be dealt with elsewhere.

In the foregoing experiments the blood was not taken from vessels draining the part of injury nor the region of operative procedure. Peripheral capillary blood resembles arterial blood in so far as potassium content is concerned; therefore the increases shown may in these cases be considered as holding good for arterial blood in general.

The data here presented agree with the postulate that potassium increases may be expected after severe tissue damage or extracellular fluid depletion, but that in a normal healthy animal it is difficult to disturb the potassium regulating mechanism.

DISCUSSION

In explanation of shock there have been many theories, each supported by extensive experimental work. For a review we refer the reader to papers by Cannon (1923), by Blalock (1936), by Meek (1936), and by Henderson (1938).

Diminished blood volume has been considered particularly important. The diminished effective blood volume might be due to fluid and electrolyte loss from the body as a whole, to capillary stasis and trapping of large amounts of blood in splanchnic or the traumatized area vascular

TABLE I

LIST OF PROTOCOLS

1. No. 3701.—Mild trauma, no shock, no K change
2. No. 3643.—Prolonged sodium amytal narcosis
3. No. 3701.—Arterial blood loss
4. No. 3707.—Repeated withdrawal of heart blood
5. No. 3752.—Repeated withdrawal of heart blood
6. No. 3755.—Repeated withdrawal of heart blood
7. No. 3641.—Mild trauma under sodium amytal anesthesia
8. No. 3644.—Trauma under amytal
9. No. 3640.—Severe trauma under amytal
10. No. 3650.—Severe trauma under ether
11. No. 3702.—Manipulation of viscera under ether
12. No. 3706.—Manipulation of viscera under ether with adrenals tied off

TABLE I (CONT'D)

PERIPHERAL WHOLE BLOOD K OF THE CAT MAY REMAIN QUITE CONSTANT NERVE BLOCKED AND TESTES CRUSHED UNDER ETHER ANESTHESIA (NO SHOCK)

Cat 3701

Jan. 11, 1937	
12:30 P.M.	26.3 mg. % K
1:45 P.M.	Operation
1:55 P.M.	27.5 mg. % K
2:00 P.M.	25.6 mg. % K
3:00 P.M.	26.3 mg. % K
4:00 P.M.	25.0 mg. % K
5:00 P.M.	25.8 mg. % K
8:20 P.M.	24.8 mg. % K
Jan. 13, 1937	Testes swollen
	29.2 mg. % K
Jan. 16, 1937	26.4 mg. % K
Jan. 19, 1937	24.4 mg. % K
Jan. 21, 1937	23.8 mg. % K

EFFECTS OF PROLONGED SODIUM AMYTAL NARCOSIS

Control Cat 3643, Weight, 2.6194 Kg.
Sex: female

TIME	RELATIVE TIME	AMOUNT OF AMYTAL ADMINISTERED	CAPILLARY BLOOD K AS MG. %	REMARKS
Oct. 22, 1936				
A.M.				
10:50	0	–	33.2	Healthy, adult cat not fasting
10:51		2.6 ml.		
11:05	15 min.	0.4 ml.		
11:15	25 min.	0.5 ml.		
11:25	35 min.			Heart rate 210; respirations, 42; temperature, 100.4
11:30	40 min.		27.2	
11:42	52 min.		29.0	Heart rate, 170; respirations, 33; temperature, 99.2; still unconscious; moves around a little
P.M.				
1:47	2 hr. 57 min.		27.1	
2:00		2.5 ml.		
2:45	3 hr. 55 min.		25.6	
4:15	5 hr. 25 min.		25.6	Has been in coma since morning; peculiar trembling condition
Oct. 23, 1936				
P.M.				
4:00	29 hr. 10 min.		27.3	Unable to move; fibrillar twitchings; drank some water after taking blood sample
Oct. 24, 1936				
A.M.				
9:30	46 hr. 40 min.		30.0	Recovered

TABLE I (CONT'D)

EFFECTS OF ARTERIAL BLOOD LOSS

Cat 3701. Weight 3.94 Kg.
Sex: Male

Feb. 15, 1937

TIME	RELATIVE TIME	AMOUNT REMOVED	WHOLE BLOOD K MG. %	SERUM POTASSIUM MG. %	SERUM CA MG. %	SPECIFIC GRAVITY WHOLE BLOOD	SERUM SP. GR.	SERUM PROTEIN GM. %
A.M.	Under light ether anesthesia femoral artery exposed for bleeding							
11:20	0	10 c.c.	–	15.4	12.9	1.0518	1.0292	7.62
11:35	15 min.	10 c.c.	21.7	16.0	12.6	1.0518	1.0289	7.52
11:45	25 min.	10 c.c.	23.0	15.3		1.0494	1.0283	7.3
11:55	35 min.	10 c.c.	21.9	14.4	11.9	1.0486	1.0278	7.13
P.M.								
12:07	47 min.	10 c.c.	22.7	15.1	11.4	–	1.0273	6.96
12:20	1 hr.	10 c.c.	21.3	13.9	11.0	1.0451	1.0251	6.2
12:30	1 hr. 10 min.	10 c.c.	23.1	17.1	10.8	1.0440	1.0255	6.33
12:40	1 hr. 20 min.	4 c.c.*	–	21.5	–	–	1.0266	6.72
			Heart's blood					
12:55	1 hr. 35 min.	10 c.c.	55.6	40.5	12.7	1.0452	1.0280	7.2
1:00	1 hr. 40 min.		Portal vein blood.—57.8 mg. % Pericardial fluid.—41.2 mg. %					

*Blood did not flow well from artery, because of very low pressure.

REPEATED WITHDRAWAL OF HEART BLOOD*

Cat 3707. Weight: 2.665 Kg.
Sex: Male

Anesthesia: none
Jan. 21, 1937

TIME	AMOUNT REMOVED	WHOLE BLOOD K MG. %	SERUM K MG. %	SERUM SPECIFIC GRAVITY	SERUM PROTEIN GM. %	REMARKS
Jan. 20 7:20		28.8(c)†				Fasting, healthy, adult cat
Jan. 21 12:20						Tied on board for experiment
12:30	10 c.c.	26.8	–	1.0293	7.6	
12:45	10 c.c.	26.4	22.2	1.0284	7.3	
1:05	16 c.c.	–	25.3	1.0266	6.7	
1:15	14 c.c.	29.4	23.3	1.0268	6.8	Air hunger
1:30	16 c.c.	32.3	25.3	1.0269	6.8	
1:50	10 c.c.	26.7	20.4	1.0254	6.3	Nictitating membrane out
2:05	10 c.c.	–	28.1	1.0259	6.5	Extremities cold
2:25						Convulsion
2:26	10 c.c.	57.4	41.7	1.0265	6.6	Very weak; gasping for air
2:30						Dead
	Total 96 c.c.					

*Calculated original blood volume: 160 c.c.
†(c)—Capillary blood.

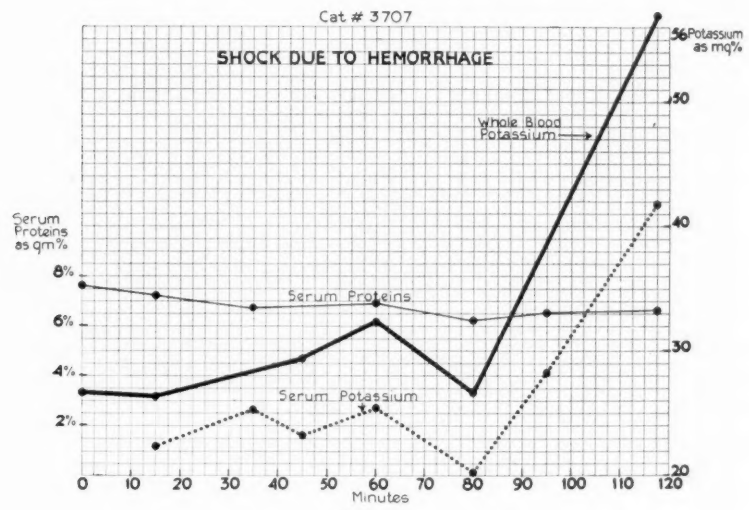

Fig. 1.

TABLE I (CONT'D)

EFFECT OF REPEATED WITHDRAWAL OF HEART BLOOD ON SPECIFIC GRAVITY OF BLOOD, BLOOD PRESSURE, SERUM, AND WHOLE BLOOD POTASSIUM

Cat 3752. Adult, male
Dec. 17, 1937

TIME	AMOUNT BLOOD REMOVED	WHOLE BLOOD K MG. % HEART	SERUM K MG. % HEART	SPECIFIC GRAVITY BLOOD HEART	BLOOD PRESSURE SYSTOLIC	REMARKS
P.M.						
3:50	(Tied on board and, under local anesthetic, femoral artery exposed for recording blood pressure)					
4:00					120	
4:05	10 c.c.	22.6	19.4	1.0473		Blood from heart
4:10					136	
4:17					154	
4:20	10 c.c.	20.4	17.6	1.0463		Blood from heart
4:25					110	
4:30	10 c.c.	20.8	17.7	1.0448	110	Blood from heart; beginning of panting
4:35					98	Blood from heart
4:40	10 c.c.	16.4	15.9	1.0435	85	Passed urine
4:45					88	
4:50	5 c.c.	18.3	18.2	–	58	Blood from heart
4:52					62	Marked panting with tongue out
5:05					78	
5:10	10 c.c.	17.8	18.3	1.0403	64	Blood from heart
5:15					40	
5:20				1.0380	44	Blood from femoral artery
5:22	10 c.c.	16.6	15.7	1.0395	40	Pallor of tongue and mucous membranes; panting; sluggish response to stimuli; allowed to remain in this state
6:45	10 c.c.	48.1	45.7	1.0449	0	Blood withdrawn just as animal expired

TABLE I (CONT'D)

EFFECT OF REPEATED WITHDRAWAL OF HEART BLOOD

Cat 3755. Weight: 3.911 Kg.
Sex: male

Anesthesia: local
Dec. 11, 1937

TIME	AMOUNT REMOVED	WHOLE BLOOD K MG. %	SERUM K MG. %	SERUM SPECIFIC GRAVITY	SERUM PROTEIN GM. %	SYSTOLIC BLOOD PRESSURE	REMARKS
A.M.							
10:45							Tied on board
10:50	10 c.c.	23.5	17.4	1.0274	6.97		
10:55							Femoral artery exposed
11:07						80	
11:10		19.1	16.3	1.0263	6.60		Quiet; respirations, 34
11:20	2 c.c.	17.6				80	
11:30	10 c.c.	18.6	15.8	1.0276	7.04		
11:45						70	
11:47	10 c.c.	19.5	17.3	1.0272	6.90		Panting; respirations, 60; nictitating membrane out
11:56	5 c.c.	17.0	15.7	1.0273	6.94	74	Panting; respirations, 190 per min.
P.M.							
12:00						74	Restless
12:10	10 c.c.	19.4	14.3	1.0264	6.63	64	Restless; struggling; respirations, 210
12:15						60	Struggling and panting; very restless
12:30	5 c.c.	–	14.2	1.0258	6.43	50	Blood clotted on taking
12:47	10 c.c.	–	12.9	1.0259	6.46		Struggling; panting and very restless; blood clotted immediately
12:52	10 c.c.	–	18.1	1.0261	6.53	44	Mucous membranes pale; blood clotted immediately
1:02	10 c.c.	25.0	19.8	1.0261	6.53		Moribund
1:05							Dead

Cerebrospinal fluid from cisterna magna clear
Potassium content: 33:2 mg. %

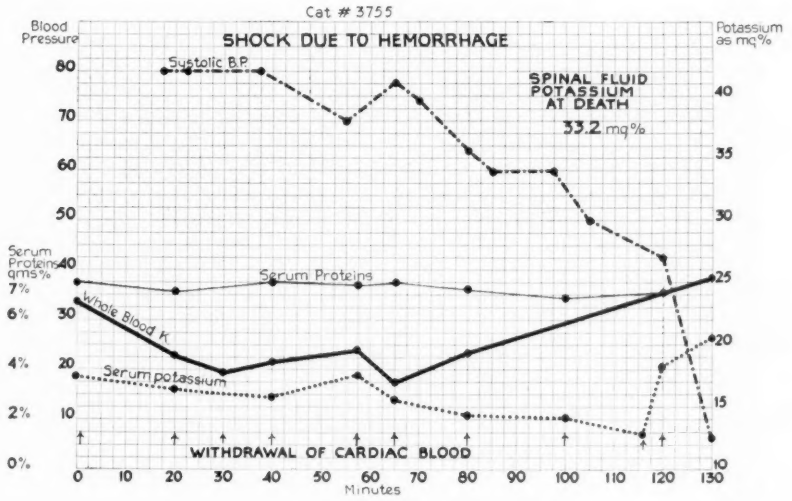

Fig. 2.

TABLE I (CONT'D)

MILD TRAUMA UNDER SODIUM AMYTAL ANESTHESIA
(70 MG./KG. 1.61 ML. AND 1 ML.)

Cat 3641. Weight: 2,300 Kg.
Sex: female

Oct. 13, 1936

TIME	RELATIVE TIME AFTER TRAUMA	BLOOD K MG. %	SPECIFIC GRAVITY WHOLE BLOOD	REMARKS
A.M.				
9:49				1.61 ml. Na amytal intraperitoneal
11:05				Cannulation of carotid completed
11:30				1 ml. Na amytal intraperitoneal
11:45	0	21.6	1.0440	
P.M.				
12:00	0	17.3	1.0469	Pound thighs with rubber hammer at 10-min. intervals.
12:14				
12:17	17 min.	14.1	1.0479	
12:25				
12:35				
12:50	50 min.	15.7	1.0481	
1:00	1 hr.*	21.1	(h 1.0486 1.0481	Died suddenly during trouble with (h) clotted canula

*No marked K changes in 1 hr. with amytal and pounding; cf. Seeley et al.

TABLE I (CONT'D)

TRAUMA UNDER AMYTAL*

Cat 3644. Weight: 3,600 Kg.
Sex: female
Oct. 22, 1936

TIME	RELATIVE TIME AFTER INJECTION OF AMYTAL	WHOLE BLOOD K MG. %	REMARKS
A.M.			
11:00	0	27.5	Healthy, adult, female 2.5 ml. 10% Na amytal (70 mg. kg.)
11:18	18 min.	24.8	Animal unconscious
11:25			Temperature, 99.6°; heart rate, 200; respirations, 24
11:35			Crushed left hind leg by pounding
11:37	37 min.	26.3	
P.M.			
12:30	1 hr. 30 min.	22.9	
12:40			Right thigh pounded
12:45			Temperature, 97.8°; heart rate, 171; respirations, 26
1:00	2 hr.	24.7	
1:30	2 hr. 30 min.	24.3	Temperature, 99.0°; heart rate, 198; respirations, 40

*No change in K under amytal in spite of pounding of legs.

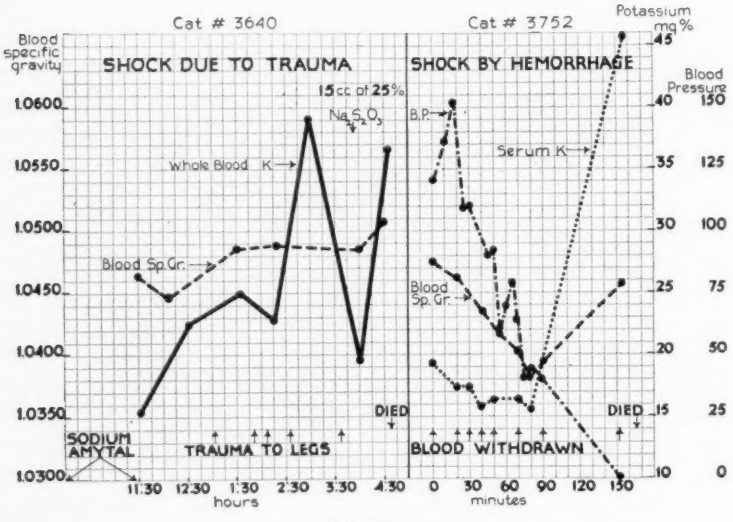

Fig. 3.

TABLE I—CONT'D

SEVERE TRAUMA UNDER AMYTAL

Cat 3640. Weight: 2.522 Kg.
Sex: female
Anesthesia: sodium amytal (70 mg./kg.)

Oct. 13, 1936

TIME	RELATIVE TIME AFTER TRAUMATIZATION	WHOLE BLOOD K AS MG. %	SPECIFIC GRAVITY WHOLE BLOOD	SYSTOLIC BLOOD PRESSURE	TEMPERATURE (RECTAL)	PULSE	REMARKS
A.M.							
9:47							1.76 ml. Na amytal intraperitoneal
10:30							Cannulation of carotid finished; 10 ml. blood lost
11:25	0	15.2	1.0462	120			1 ml. Na amytal intraperitoneally
P.M.							
12:30	0	22.1	1.0447				
12:45					96°		Crush and pound left hind leg
1:20	35 min.	24.8	1.0486		95.8°		
1:33					95.0°		
1:35							Pound both legs
1:46							Pound both legs
1:58					96.1°		
2:10	1 hr. 25 min.	22.5	1.0487				
2:25				110			Pound both legs
2:40	1 hr. 55 min.	39.4	1.0485			120	
3:05				110	101.0°		Pound both legs
3:07							Pound both legs
3:25							Anticoagulant 25% $Na_2S_2O_3$ run in
3:28				130			
3:55				85	101.4°		
4:00	3 hr. 15 min.	19.3	1.0487				
4:25				60	101.6°	160	
4:30	3 hr. 45 min.	36.5(h)	1.0496(h)	60	103.0°		
4:33							Dead

TABLE I (CONT'D)

EFFECT OF SEVERE MUSCLE TRAUMA AND MULTIPLE FRACTURES UNDER ETHER

Cat 3650. Weight: 3.686 Kg.
Sex: male, adult

Dec. 7, 1936

TIME	RELATIVE TIME	CAPILLARY BLOOD K AS MG. %	SPECIFIC GRAVITY CAPILLARY BLOOD	WEIGHT % LOSS	REMARKS
P.M.					
2:30		33.8	1.0525		Fasting
3:10	0	Under ether anesthesia, both hind legs crushed			
3:20	10 min.	29.9	1.0579		Respirations, 104
3:40	30 min.	38.2	1.0566		Respirations, 190; panting
4:10	1 hr.	36.6	1.0568	3.600 –2.5%	
5:10	2 hr.	34.2			Restless
6:15	3 hr. 5 min.	29.7	1.0576		
7:10	4 hr.	23.1	1.0587	3.572 –3.2%	Ears cold; blood dark and flows slowly
7:25					Respirations, 38
7:45	4 hr. 35 min.	28.6	1.0601		Blood very dark; respirations, 35
8:25	5 hr. 15 min.	33.5	1.0568	3.560 –3.5%	Ears and extremities cold
9:20	6 hr. 10 min.	35.8	1.0553	3.543 –4.0%	
9:40	6 hr. 30 min.	Under ether anesthesia, right front leg crushed			
9:45	6 hr. 35 min.		1.0553		
10:00	6 hr. 50 min.	25.7			Respirations, 40
10:25	7 hr. 15 min.	29.3	1.0556		Much salivation
10:55	7 hr. 45 min.	27.0	1.0551	3.500 –5.0%	
11:50	8 hr. 40 min.	30.0	1.0550		Blood flow poor; pulse, 200
Dec. 8					
A.M.					
12:50	9 hr. 40 min.	33.6	1.0565	3.500 –5.0%	Blood clots readily
2:10	11 hr.	28.7	1.0560		Condition same
3:10	12 hr.	29.9	1.0560		
4:10	13 hr.	31.3	1.0560	3.450 –6.5%	
4:15	13 hr. 5 min.				Pericardial fluid, 49.8 mg. %
		Heart blood			
4:18	13 hr. 8 min.	31.5			5 c.c. withdrawn
4:40	13 hr. 30 min.	Ether anesthesia, legs traumatized and massaged			
4:55	13 hr. 45 min.	28.0	1.0547		Convulsion

TABLE 1 (CONT'D)

EFFECT OF SEVERE MUSCLE TRAUMA AND MULTIPLE FRACTURES UNDER ETHER—CONT'D

TIME	RELATIVE TIME	CAPILLARY BLOOD K AS MG. %	SPECIFIC GRAVITY CAPILLARY BLOOD	WEIGHT % LOSS	REMARKS
5:35	14 hr. 25 min.	33.0	1.0568		Legs massaged; respirations, 112 irregular
6:10	15 hr.	40.5			
6:15	15 hr. 5 min.				Dead

Autopsy.—Severe muscle trauma with some extravasation of blood; ruptured muscles very dry
Compound fracture of both right and left humerus
Compound fracture of right femur
Compound fracture of left tibia and fibula
Lungs: collapsed; petechial hemorrhages on surface
Heart: in diastole
Stomach: dilated; contained hair ball but not fluid
Small intestine: cyanotic
Large intestine: filled with hard feces
Liver: red, soft, slightly mottled
Spleen: red, leathery in consistency
Kidneys: large, soft, pale brown
Adrenals: soft, tan color
Bladder: partially filled

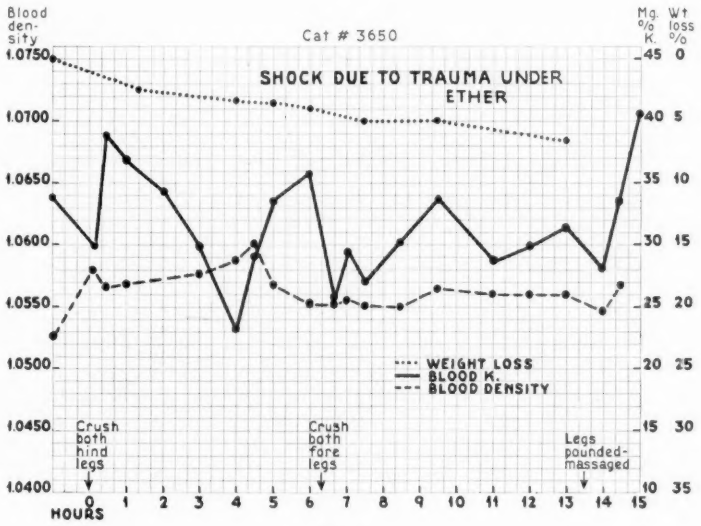

Fig. 4.

TABLE I (CONT'D)

EFFECTS OF INTESTINAL MANIPULATION

Cat 3702. Weight: 3.657 Kg.
Sex: male
Anesthesia: ether

Jan. 11, 1937

TIME	RELATIVE TIME AFTER MANIPULATION	CAPILLARY WHOLE BLOOD K AS MG. %	SPECIFIC GRAVITY CAPILLARY BLOOD	REMARKS
Jan. 9				
5:45	0	26.0	–	Fresh, healthy adult
Jan. 11				
P.M.				
12:40	0	25.0	1.0512	Nonfasting; weight, 3856 gm.
12:45	Operation under ether; viscera manipulated in a towel for 25 min.;			
1:15	abdomen closed; weight, 3,800 gm.			
1:20	5 min.	24.9	1.0500	Respirations, 180
1:35				Respirations, 260; urinated and vomited much food
2:20	1 hr. 5 min.	19.6	1.0483	Respirations, 182; vomited thin brownish fluid
2:20				Weight, 3,457 gm.
3:20	2 hr. 5 min.	22.9	1.0512	Weight, 3,429 gm.; mucous membranes dry
3:40				Respirations 60, irregular; weight: 3,417 gm.
4:20	3 hr. 5 min.	34.3	1.0529	Respirations 100; blood obtained with some difficulty
		Heart blood	Heart blood	
5:00	3 hr. 45 min.	24.2	1.0508	
		Heart serum		
6:30	5 hr. 15 min.	26.0	1.0535	
		Heart blood		
7:45	6 hr. 30 min.	41.0	1.0518	Dead
		Peritoneal fluid		
		57.1		

Autopsy.—Peritoneal cavity filled with bloody fluid. Intestines contracted. Much subserosal ecchymoses where gut was handled. Liver and spleen leathery in consistency. Gall bladder filled. Pancreas pale. Kidneys tense and swollen. Adrenal cortex gray and shrunken; hemorrhage between cortex and medulla. Heart in diastole. Lungs pink and collapsed with few petechial hemorrhages on surface.

TABLE I (CONT'D)

EFFECT OF MANIPULATION OF INTESTINES WITH ADRENALS TIED OFF

Cat 3706. Weight: 3.742 Kg.
Sex: male
Anesthesia: ether

Jan. 21, 1937

TIME	RELATIVE TIME	CAPILLARY BLOOD K AS MG. %	CAPILLARY BLOOD SPECIFIC GRAVITY	REMARKS
Jan. 20				
7:15		25.8		Healthy, adult, nonfasting cat
Jan. 21				
A.M.				
11:00	0	22.1	1.0553	Fasting; tied on board
11:15				Ether anesthesia, operation
11:25				Both adrenal glands tied off
11:30	15 min.	17.6	1.0551	Heart rate, 220; respirations, 28
				Rough manipulation of intestines
11:45	30 min.			Operation finished
11:50	35 min.	21.4	1.0483	Nictitating membranes out
P.M.				
12:15	1 hr.	28.3		Recovered from anesthesia. Marked asthenia; some oozing of blood from wound
12:45	1 hr. 30 min.	19.5	1.0498	Defecated
1:35	2 hr. 20 min.	22.1		Struggled
2:10	2 hr. 55 min.	38.5	1.0528	Extremities cold; in shock
		Heart blood	Heart blood specific gravity	
4:00	4 hr. 45 min.	22.4	1.0503	Extremities cold
5:00	5 hr. 45 min.	25.8	1.0543	Labored breathing, rate 98; extremities cold.
5:55				Very restless
6:05	6 hr. 50 min.	30.6	1.0544	Very weak; died shortly after taking blood

Autopsy.—Lungs: collapsed, pink; no fluid in pleural cavity
Heart: some bloody fluid found in pericardial cavity
Peritoneal cavity: much bloody fluid; serosa showed trauma, with extravasation of blood
Intestines: contracted with extensive subserosal hemorrhage; thin fibrinous adhesions present; the ligatured adrenals pale
Kidneys: soft, swollen, brown in color; bladder filled

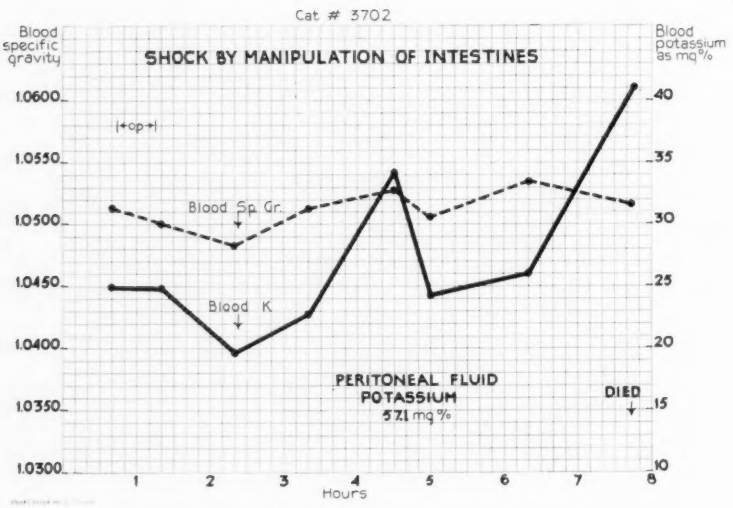

Fig. 5.

beds, to capillary leakage and filling of tissue spaces, or finally to a loss of extracellular body fluids by hydration of cells. Maintenance of a constant body weight would favor the explanations of internal redistribution; whereas, a weight decrease would strengthen the view of anhydremia by actual fluid loss from the body.

Others believe that the presence of some toxin is necessary to explain all of the phenomena. This toxin was first thought to be histamine, but the term "H" substance is now generally used for this histamine-like constituent of tissues which is released by injury. It is probable that potassium is an important "H" substance always available.

The relation of adrenal cortex function to shock is attested by an extensive literature. Treatments of various types of shock, such as traumatic (Swingle and Parkins, 1935), anaphylactic (Wolfram and Zwemer, 1935; Dragstedt and others, 1937), histamine (Wyman and Tum Suden, 1937), and the toxin of intestinal obstruction (Heuer and Andrus, 1934; Wohl and others, 1937) are represented. The evidence that potassium regulation is a function of the adrenal cortex (Zwemer and Sullivan, 1934; Zwemer and Truszkowski, 1936, 1937; Truszkowski and Zwemer, 1938) is receiving increasing support (Allers, 1936; Harrop, 1936; Nilson, 1937; Thorn, 1937). Since a marked increase in extracellular potassium is injurious to cells and injured cells lose potassium, a vicious cycle ending in death may be initiated if the plasma K is allowed to rise. Therefore, rational therapy for shock should include measures which enable the body to restore and maintain a normal potassium level in body fluids. These are sodium salt therapy, adequate but not excessive fluid administration (Scudder, Zwemer, and Whipple, 1938), and cortin therapy.

TABLE II

WHOLE BLOOD K IN SECONDARY SHOCK IN CATS

CAT NO.	INITIAL K MG. %	PROCEDURE USED TO PRODUCE SHOCK	TIME OF SURVIVAL	K VALUE IN SHOCK MG. %	TOTAL NUMBER OF SAMPLES TAKEN
3655	27.7	50 cm. strangulated loop	9 hr.	36.4	9
3630	27.5	Jejunal loop	14 hr.	39.3	9
3631	20.2	20 cm. strangulated loop	30 hr.	66.6	15
3632	17.3	Anemic jejunum loop	45 hr.	29.6	5
3713	22.7	Duodenostomy	3 days	44.2	11
3636	30.0	Esophageal obstruction	3½ days	52.0	11
3639	21.8	Duodenal obstruction	3½ days	39.7	11
3718	35.6	Duodenostomy	4 days	61.5	18
3712	29.1	Jejunostomy	4 days	84.0	9
3717	37.1	Jejunostomy	4 days	86.6	9
3721	25.5	Gastrostomy	5 days	37.5	11
3724	22.6	Gastrostomy	5 days	40.9	16
3709	19.8	Ileostomy	5 days	84.8	10
3649	24.3	Pancreatitis	5 days	52.3	10
3638	31.7	Duodenal obstruction	7½ days	42.6	16
3710	21.1	Ileostomy	10 days	48.0	21

In attempting to correlate the divergent theories concerning the causes of death in adrenal insufficiency (Zwemer and Truszkowski, 1937), intestinal obstruction (Scudder, Zwemer, and Truszkowski, 1937), and intestinal fistulas (Scudder and Zwemer, 1937) consideration of potassium as the unknown toxin seemed to make the various explanations more compatible. Since in a condition of shock our present data show a rise in blood potassium to high levels, it seems reasonable to believe that inadequate potassium regulation is also a factor which must be considered in any explanation of shock.

SUMMARY

The remarkably constant regulation of potassium by the body is altered during the condition of shock. Fluctuations suggest alternate success and failure of regulation, and a sudden increase precedes death. Peripheral blood samples are not always indicative of the changes taking place internally, especially in the fluids of closed cavities, such as pericardial and cerebrospinal fluids (Table III).

TABLE III

POTASSIUM CONTENT OF SOME BODY FLUIDS AT TIME OF DEATH FROM SHOCK

Cerebrospinal fluid	32.9 mg. % K
Lymph	30.3 mg. % K
Pericardial fluid	49.8 mg. % K
Peritoneal fluid	57.1 mg. % K
Traumatized tissue fluid	77.9 mg. % K

Detailed data from twelve cats (Table I), and supplementary information from sixteen other animals (Table II) are presented.

We take this opportunity to thank Dr. Richard Truszkowski for his assistance in the amytal experiments.

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STUDIES OF SODIUM, POTASSIUM, AND CHLORIDES OF BLOOD SERUM IN EXPERIMENTAL TRAUMATIC SHOCK, SHOCK OF INDUCED HYPERPYREXIA, HIGH INTESTINAL OBSTRUCTION, AND DUODENAL FISTULAS

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IN VIEW of the profound disturbances of tissue metabolism, blood volume, and water balance associated with traumatic shock, hyperthermic shock, and high intestinal obstruction, chemical alterations of the blood would seem inevitable. There has accumulated much evidence to show that this is true.

This investigation had for its purpose the determination of the extent to which certain of these changes, namely the alterations in the relative proportions of serum sodium and potassium, play in the production of symptoms and in the cause of death. It will be observed from an analysis of the results that there exists no constant relationship, also that the quantitative changes in both sodium and potassium appear to be incidental to the changes in blood volume and concentration rather than the cause of the prostration and death.

EXPERIMENTS

Sixteen dogs were used for nineteen experiments. Chemical analyses were made upon blood serum from blood aspirated from the heart. In one animal, for purposes of comparison, determinations were made upon both whole blood and serum from samples of blood taken simultaneously. Contrary to certain reports, we found a wide variation in the content of sodium and potassium in serum as compared to whole blood. Blood chlorides were determined by the method described by Saifer and Kornblum and the sodium and potassium by a modification of the methods of Kramer and Tisdall and Saht described by Morgulis and Perley. With only a few exceptions, each analysis was run in duplicate.

TRAUMATIC SHOCK

After taking blood for normal control determinations, 3 animals were anesthetized with ether and traumatic shock was induced by contusing both lower extremities. In 2 animals, Dogs 1R and 2R, the trachea and carotid artery were cannulated and connected to record-

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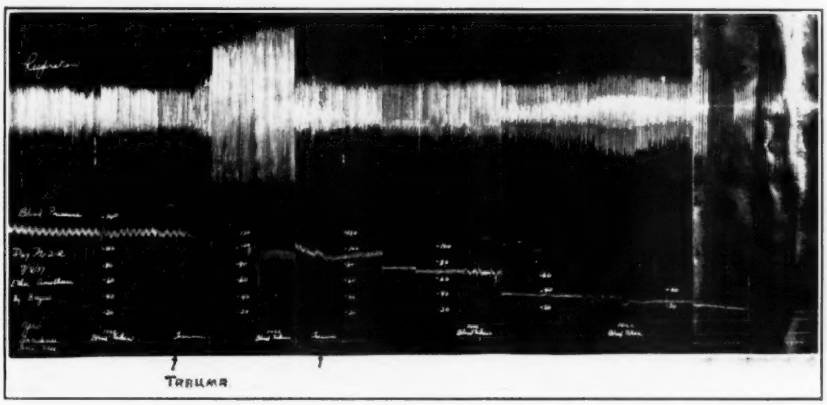
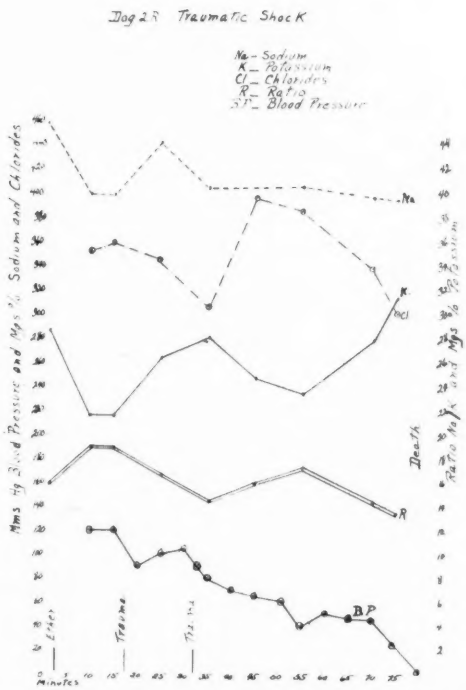
ing manometers mounted on a kymograph. Continuous records of respiration, pulse rate and blood pressure were made throughout the experiments. Portions of these records are shown in Figs. 1*A* and 2*A*.

Because sodium citrate was used in the system connecting the carotid artery and manometer, it was possible for minute quantities of sodium



A.

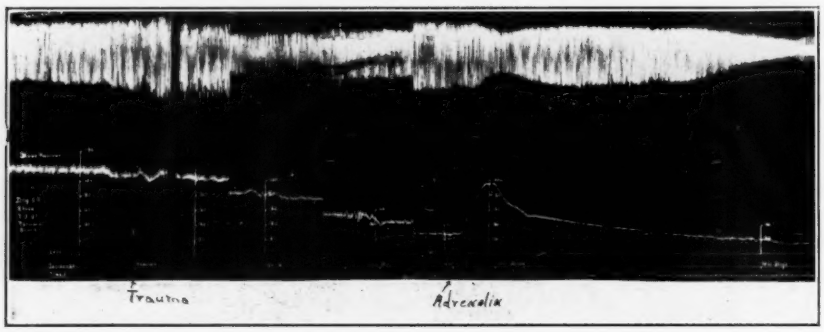


B.

Fig. 1.—Dog 2R. *A*, Sections from a continuous kymographic record showing changes of pulse, blood pressure, and respiration with progressive development of traumatic shock. *B*, Graphic record of changes of blood pressure recorded in *A* and of serum sodium, potassium, and chlorides during the development of traumatic shock. Note fall of sodium and potassium with induction of ether anesthesia, a sharp rise to nearly normal levels after trauma and, after a second recession, a rise of potassium to a level slightly above normal as shock became profound.

to enter the blood stream. For this reason the blood studies in the third animal, Dog 4L, were made without recording blood pressure. Since in this animal the analyses did not differ significantly from those in which blood pressure records were made, it would appear that if sodium entered the blood stream it did so in too small quantities to influence the levels of sodium and potassium of the serum.

A.



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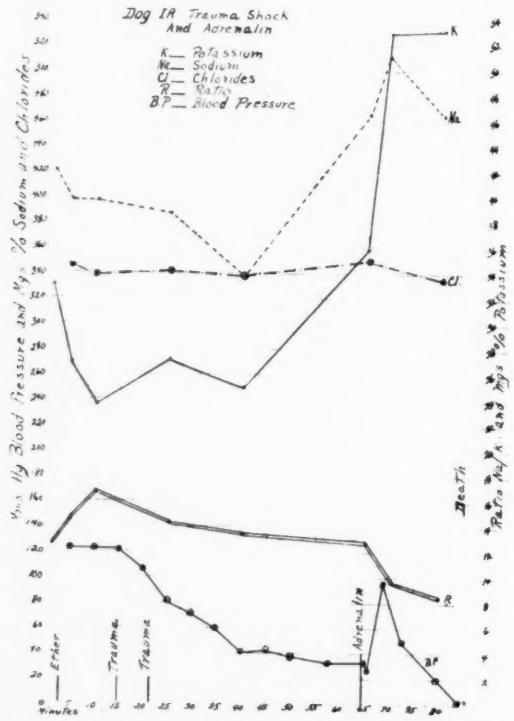


Fig. 2.—Dog 1R. *A*, Sections from a continuous kymographic record of induced traumatic shock. When the blood pressure had fallen to 30 mm. Hg, 7 mins. of adrenalin was given intracardially. Immediately the pressure rose to 95 mm. and then fell progressively to zero with death. *B*, Plotted with the blood pressure curve taken from the kymographic record illustrated in *A* are the concomitant fluctuation of serum sodium, potassium, and chlorides. Note the initial fall of sodium and potassium with induction of anesthesia, the gradual return to preoperative levels with development of shock, and then the precipitous rise to very high levels with the elevation of blood pressure which followed injection of adrenalin.

Detailed analyses of the results of the experiments are shown in Figs. 1*A* and *B*, 2*A* and *B*. They consistently showed the following changes: (1) A sharp fall of both sodium and potassium with the induction of ether anesthesia. (2) A slight rise but continued subnormal level of both sodium and potassium with the progressive fall in blood pressure until the degree of shock became profound and terminal. There was then a sharp rise of potassium in all animals. In one, Dog 1R, it mounted to an extremely high level; in another, Dog 2R, to a level slightly above the preoperative level; and in the third, Dog 4L, it never reached the preoperative level. In Dog 1R adrenalin was given intracardially 1½ minutes before the first blood sample, which showed a very high level of potassium, was taken. In this case we believe that the adrenalin was probably at least partially responsible for this response because simultaneously there was a precipitous rise of blood pressure. (3) No significant changes in blood chlorides. (4) The sodium-potassium ratio rose with induction of anesthesia and progressively fell as the blood pressure dropped.

INDUCED HYPERPYREXIA

In 4 dogs fever was induced and made to progress to a lethal degree in a heat chamber of Kettering design. As in the preceding experiment, continuous kymographic records were made of respirations, pulse, and blood pressure in 2 animals but omitted in 2 dogs to avoid the possible influence of the sodium in sodium citrate used in the manometric system. The anesthesia consisted of amytal administered orally and supplemented by ether induction.

Composite data of the experimental results are shown in Fig. 3*A* and *B* and in Tables I and II. They may be summarized as follows: (1) Induced fever became lethal at 112° F. (2) Blood pressure began to fall as the temperatures reached 104° and fell rapidly to shock levels as temperatures mounted above 108°. (3) Potassium fell with the induction of anesthesia and then rose to levels of 30 to 50 per cent above the normal control levels with the induction of fever.

TABLE I

DOG 500—HYPERTHERMIC SHOCK

	RECTAL TEMPERATURE	SODIUM MG. %	CHLORIDES MG. %	POTASSIUM MG. %	CALCIUM MG. %
1. Normal control	100.8	270	359	15.2	11.2
2. After induction of anesthesia		274	347	14.2	11.46
3. Hyperthermia, 30 min.	108.2	245	353	12.8	10.70
4. Hyperthermia, 55 min.	110.2	267	374	20.2	9.83
Experimental error		+ or −5%	+ or −2%	+ or −3%	+ or −1%

TABLE II

DOG 502—HYPERTHERMIC SHOCK

	RECTAL TEMPERATURE	SODIUM MG. %	CHLORIDES MG. %	POTASSIUM MG. %	CALCIUM MG. %
1. Normal control	101.4	286	368	12.4	9.92
2. After induction of anesthesia		274	354	12.5	11.1
3. Hyperthermia, 40 min.	106.0	254	360	6.5	10.37
4. Hyperthermia, 55 min.	106.8	262	371	8.3	10.65
5. Hyperthermia, 60 min.	107.5	255	373	10.5	10.46
6. Hyperthermia, 65 min.	108.0	258	375	12.9	10.24
7. Hyperthermia, 90 min.	110.0	282	373	12.9	10.15
8. Hyperthermia, 115 min.	111.8	282	380	14.9	10.18
Experiment error		+ or −4%	+ or −2%	+ or −5%	+ or −1%

The rise in potassium roughly paralleled the rise in fever in 3 animals, but in 1 it reached a maximum at a temperature of 106° and, although it then fell, it remained above the control level until the animal was in extremis. (4) Sodium and chlorides remained relatively unchanged in 3 dogs. In 1 the sodium fell consistently, falling to nearly one-half of its control level. (5) The sodium-potassium ratio showed a slight rise with induction of anesthesia and a fall with development of fever and shock.

Determinations of serum calcium were made in 2 dogs. In both a slight rise with induction of anesthesia was followed by a slight fall to the normal initial level or slightly below it.

INFLUENCE OF ETHER ANESTHESIA AND ADRENALIN

Determinations of these influences were undertaken because the serum potassium had shown a sharp drop constantly and consistently with induction of ether anesthesia in the experiments described above and had mounted to an excessively high level immediately after the administration of adrenalin in the one dog which received it while in profound shock.

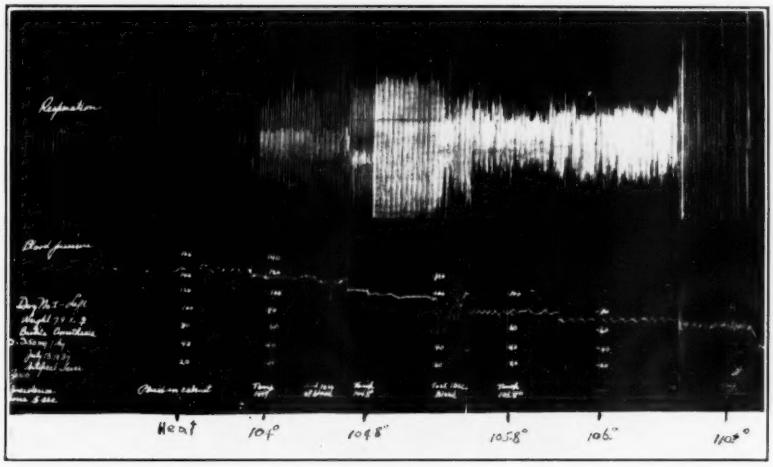
The results are shown in the graphs, Fig. 4*A-C*. With both ether and adrenalin, potassium fell sharply but transiently and returned promptly to the normal control levels. At no time did the potassium rise above the normal control levels. Sodium and chlorides showed no significant change. The ratios of sodium and potassium varied inversely with the fluctuations of potassium.

HIGH INTESTINAL OBSTRUCTION

At varying levels and by various means, the duodenum was completely obstructed in 5 animals and the duodenum and proximal jejunum in 2 animals.

1. *Obstruction by Division.*—In 2 dogs obstruction was produced by severing the bowel and turning in the ends with two rows of sutures. In 1 dog the obstruction was made just below the pylorus; in the

A.



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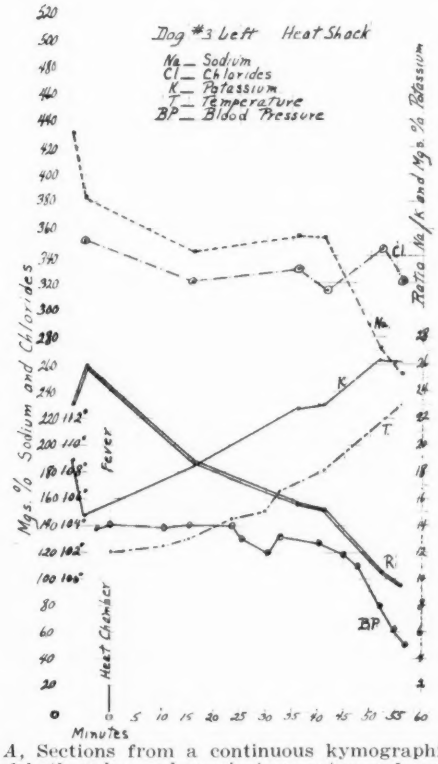


Fig. 3.—Dog 3L. *A*, Sections from a continuous kymographic record showing the progressive increase of both pulse and respiratory rates and progressive fall of blood pressure associated with the increasing hyperpyrexia. Respirations became profoundly increased in respect to both rate and amplitude. *B*, A composite graph of changes in blood pressure, body temperature, and blood chemistry during the course of development of hyperpyrexia to its fatal termination. Note the parallel rises of temperature and potassium.

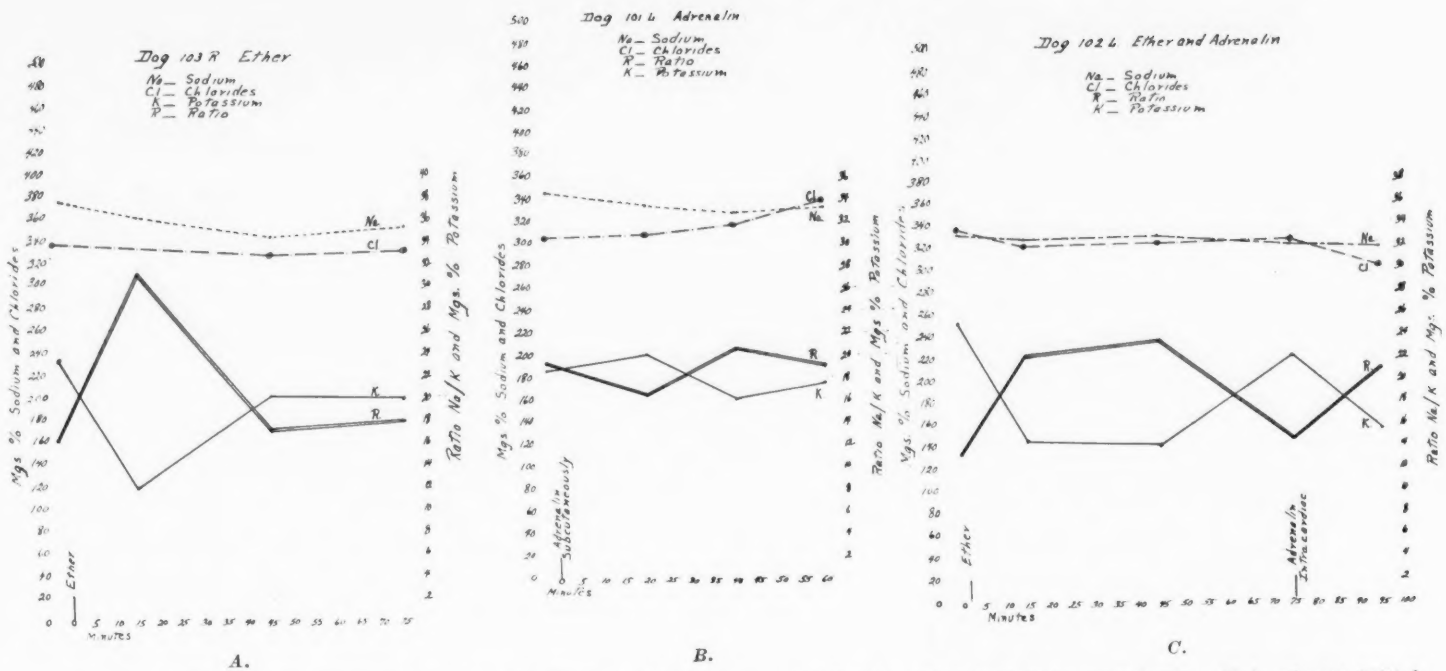


Fig. 4.—*A*, Changes in serum sodium, potassium, and chlorides associated with ether inhalation anesthesia. Note abrupt initial drops followed by a rise but failure to regain the normal preoperative levels. *B*, Changes in serum sodium, potassium, and chlorides following subcutaneous administration of 1 c.c. of adrenalin, 1:1,000. Note slight fall in potassium. *C*, The response to both ether inhalation anesthesia and adrenalin. After the serum potassium had returned almost to its original normal preanesthetic level, 0.5 c.c. of adrenalin, 1:1,000, was given intracardially. Note that this was followed immediately by a second drop in the level of potassium.

other, a few centimeters below the ampulla of Vater. Thus, in the dog with pyloric obstruction only gastric secretions were excluded from the intestinal tract. Bile and pancreatic and intestinal secretions could move down the tract unobstructed, but in the latter animal all of these secretions likewise were excluded. However, the dog with

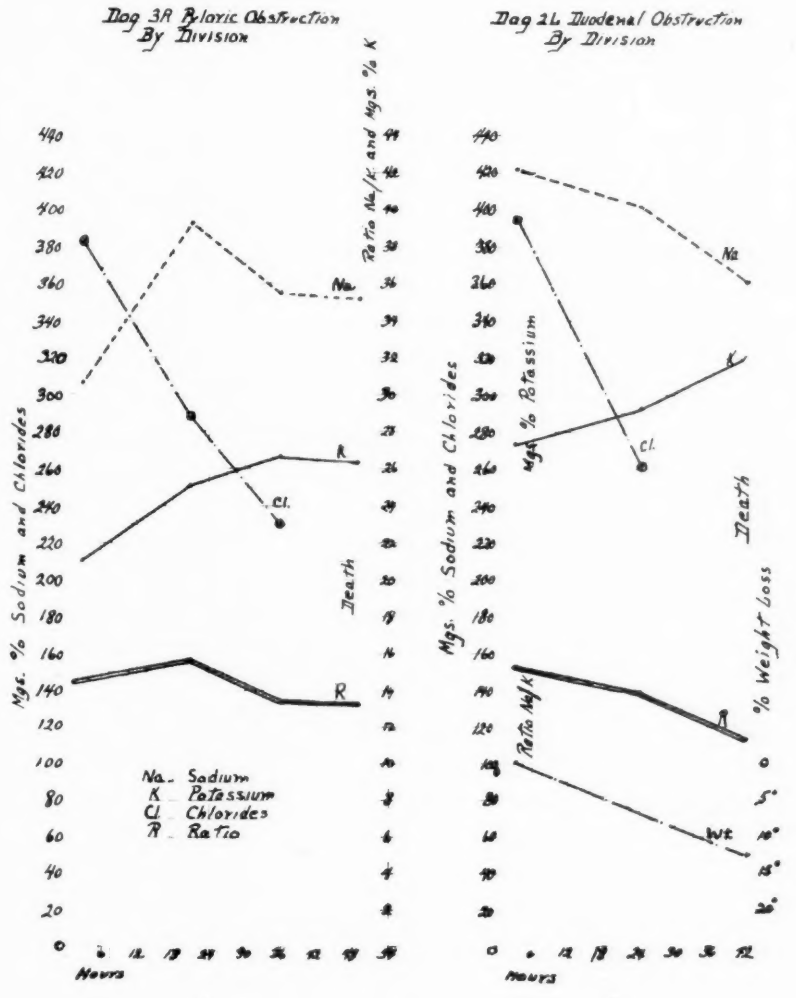


Fig. 5.—*A*, Pyloric obstruction by division. Note the large decrease in chlorides and a small but sustained increase of potassium. *B*, Duodenal obstruction by division; a marked decrease in chlorides and a small progressive increase in potassium.

obstruction above the ampulla lived 52 hours, 10 hours longer than the one obstructed below it.

As shown in the Protocols 1 and 2 and in Fig. 5*A* and *B*, there was consistently a precipitous fall in chlorides, a rise of potassium to 18 and 26 per cent above preoperative levels, and a slight fall in the sodium-potassium ratio. In the animal with pyloric obstruction there

was a rise in sodium, while in the one with obstruction below the ampulla of Vater the sodium fell progressively. The latter animal lost 13 per cent of its body weight.

PROTOCOL 1

PYLORIC OBSTRUCTION BY DIVISION

Dog 3R, male; weight, 12.3 kilo. On July 22, 1937, the duodenum was divided immediately distal to the pyloric sphincter and the ends were closed by inversion.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	102.0	382	307	21
9	Considerable vomiting; dry and slightly apathetic	102.8	288	393	25
26	Weak, unsteady gait; apathetic, dry, gaunt	104.0			
42	Stands unwillingly; eyes contain mucus; muscles twitch	103.0	230	355	26.6
50	Refuses to stand; muscles twitch	101.9		350	26.4
60	Death—Autopsy: peritoneal cavity clean, suture lines tight, stomach contracted, duodenum distended, heart normal, terminal bronchopneumonia both lungs				

2. *Obstruction by Simple Ligation.*—In 3 dogs the duodenum was obstructed immediately below the ampulla of Vater by simple ligation with broad strands of cotton tape. There was no interference with circulation. In all dogs the tape cut through the bowel, resulting in leakage and peritonitis in 1 dog, while in the other 2 the obstruc-

PROTOCOL 2

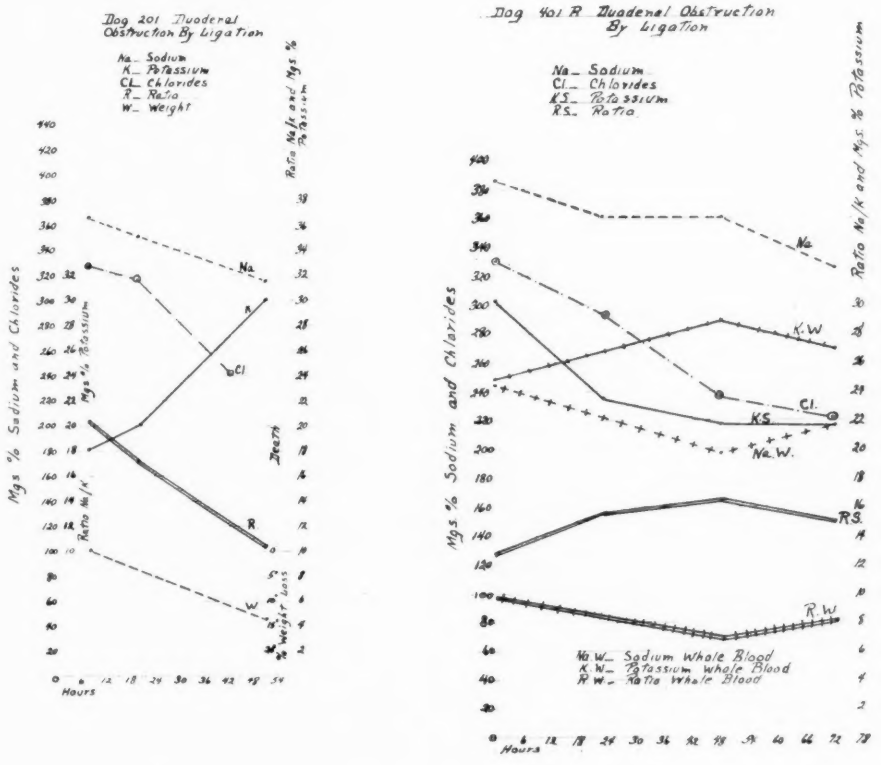
DUODENAL OBSTRUCTION BY DIVISION

Dog 2L, male; weight, 14.47 kilo. On July 22, 1937, the duodenum was divided 5 cm. below the ampulla of Vater and the ends were turned in.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	101.8	395	422	27.4
18	Vomiting several times; apathy; dehydrated	102.2			
25	Some, but less vomiting; weak, but stands and wags tail slowly	104.0	261	403	29.2
42	Very weak, listless and unable to stand; eyes coated with mucus; irregular twitching of all the muscles	100.0		361	32.0
43	Dead—Autopsy: abdomen dry and clean, suture lines tight, stomach and duodenum collapsed, below obstruction bowel slightly dilated; lungs clear, heart normal				

tion was released and spontaneous anastomosis occurred. The latter animals, after becoming almost moribund, completely recovered.

Consistently in all of these animals there was a large and rapid fall of chlorides and a lesser fall of sodium. Potassium increased from 18 to 30 mg. per cent in the dog which developed peritonitis but in the other 2 it not only promptly fell below the preoperative level but also remained below that level. The sodium-potassium ratios in all 3 animals varied inversely with the levels of potassium and all lost weight, 1 as much as 23 per cent. See Figs. 6*A* and *B* and 7 and Protocols 3, 4, and 5.



A. *B.*

Fig. 6.—*A*, Duodenal obstruction by ligation. A large progressive decrease in chlorides and a large terminal increase in potassium. In addition to obstruction, autopsy revealed peritonitis. *B*, Duodenal obstruction with recovery. In general this experiment parallels that illustrated in Fig. 7. Determinations of sodium and potassium were made upon both serum and whole blood. The values are in no way comparable.

The records of 2 of these dogs deserve individual comment.

Dog 101R, 96 hours after simple ligation of the duodenum 4 cm. below the ampulla of Vater, became so weak that it was unable to stand. The mouth was dry and the eyes were covered with a thick mucoid discharge. Muscle groups twitched irregularly throughout the body and there had been a loss of 17 per cent of body weight. Chlorides had fallen from 370 to 196 mg. per cent. Potassium, after

PROTOCOL 3

DUODENAL OBSTRUCTION BY SIMPLE LIGATION

Dog 201L, female; weight, 4.74 kilo. On Aug. 3, 1937, the duodenum was ligated 2 cm. distal to the ampulla of Vater with a piece of tape so placed that it did not disturb circulation.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	101.2	366	345	18.6
7	Vomiting; slightly apathetic	100.4	324	366	18.0
19	Some vomiting; dry; looks quite well	103.2	319	351	20.0
41	Weak, but stands and wags tail; dry	101.8	242		
51	Very weak, refuses to stand; scum over eyes; muscles twitch % weight loss, 13.5	102.6		314	30.0
52	Dead—Autopsy: purulent exudate throughout peritoneal cavity but peritoneum only slightly injected; ligature cut through bowel wall resulting in leakage; stomach and bowel collapsed; both lungs contained hemorrhagic areas				

an initial drop from 30.5 to 21.4 mg. per cent during the first 55 hours, had regained much of the loss but reached a maximum level of only 29 mg. per cent.

At this time the animal's death seemed imminent, but 24 hours later there was unmistakable evidence of improvement, which lasted about 48 hours. Then there developed a return of symptoms and again death seemed imminent. But at this time, 192 hours, 8 days following operation, something happened and from this time on the animal's condition constantly and rapidly improved. Subsequent exploratory operation showed that continuity of the duodenal lumen had been reestablished by spontaneous anastomosis. With the beginning of improvement on the eighth day, the animal began to take water and there followed a sharp rise of sodium and a progressive but slower rise in chlorides. There was no change in the level of the potassium until the animal began to take food 96 hours later or on the twelfth day. It then progressively mounted.

Interestingly, there was no appreciable gain in weight during the first 7 days after the beginning of improvement and of ingestion of water. Before there was a gain in weight the serum sodium and chlorides had returned to nearly normal levels.

In Dog 401R analyses of sodium and potassium were made upon both serum and whole blood from samples drawn simultaneously. The sodium of both serum and whole blood decreased and, when the values were plotted, formed similar curves. The curves of potassium, however, were completely reversed. Potassium of the serum showed a progressive decrease and that of whole blood a progressive increase.

PROTOCOL 4

DUODENAL OBSTRUCTION BY SIMPLE LIGATION

Dog 101R, female; weight, 7.03 kilo. On July 27, 1937, the duodenum was ligated with a broad piece of tape, 4 cm. distal to the ampulla of Vater.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	101.0		346	30.6
7	Vomited several times; slightly apathetic		336	366	29.0
19	Continued vomiting, dry but looks fairly well	102.2	312	362	29.2
22	Dry, weak; has taken no food and little water			371	27.6
26	No change	101.6		366	25.2
42	Vomiting less; much weaker; mucopurulent scum over the eyes	100.1	252	362	24.0
55	Weak, tremulous, very gaunt	100.0	221	332	21.4
74	Sways when standing, staggers and falls	100.4	223	312	26.6
90	Unable to stand, cold, uninterested in surroundings; twitching	100.0	209	317	26.6
105	Nearly moribund; 21% weight loss	100.0	214	321	21.6
139	Spontaneous anastomosis and release of obstruction; much improved; stands, wags tail, drinks water	100.6	209	324	19.0
176	Condition unchanged	100.4	196	293	20.4
188	Relapse, nearly moribund	100.2	196	287	14.6
234	Much improved, appears well but weak, flanks filled out; taking food	101.4	206	331	17.2
288	Continued improvement; appears quite well	102.2	227	348	18.0
360	Jumps about, appears well		309	379	23.2
405			327	375	23.6
502	Regained preoperative weight		332	380	24.7
574	Continued normal appearance	102.2	337	325	27.4

Exploratory operation showed that ligature around bowel had cut through and a spontaneous anastomosis had developed. Apparently this took place simultaneously with recovery from moribund state. As the dog began to take water, the chlorides and sodium dropped slightly, possibly from blood dilution, and then increased rapidly

From these findings, it would appear that the relative content of potassium in serum and in whole blood does not remain constant and that determinations made upon whole blood do not indicate the changes which take place in serum potassium.

PROTOCOL 5

DUODENAL OBSTRUCTION BY SIMPLE LIGATION

Dog 401R, female; weight, 7.3 kilo. Aug. 24, 1937, the duodenum was ligated 5 cm. distal to the ampulla of Vater with tape.

HOURS POST-OPERATIVELY	REMARKS	RECTAL TEMPERATURE	CHLORIDES		SODIUM		POTASSIUM	
			SERUM	WHOLE BLOOD	SERUM	WHOLE BLOOD	SERUM	WHOLE BLOOD
	Preoperative	101.2	331		386	245	30.2	24.8
24	Vomited several times; weak and dry	102.6	293		361		23.4	
48	Less vomiting; listless; wobbles when standing	101.9	238		360	198	21.8	28.9
76	Scum over eyes; generalized twitching; very weak	101.5	221		326		21.8	
90	No definite change; possibly stronger	100.8	244		365	219	20.8	26.5

From this time on the animal improved and rapidly regained normal health. At a subsequent post-mortem examination, it was found that a spontaneous anastomosis had been established around the point of obstruction

3. *Obstruction With Strangulation.*—In 2 dogs the duodenum below the ampulla of Vater and including a small upper segment of jejunum were strangulated by encircling the loop with a piece of tape which was tied with tension sufficient to cause obstruction of the bowel and of venous return but not of the arterial blood supply. The loops were 20 cm. and 12 cm. in length. The dog with the longer loop died in 18 hours, while the one with the short loop survived 27 hours. Each dog lost approximately 10 per cent of its body weight and showed no significant alteration of blood chemistry. The chlorides dropped only slightly and the sodium in each instance, after a transient, abrupt elevation, returned to the normal preoperative levels. Potassium in the dog with the long loop remained unchanged; in the other one it

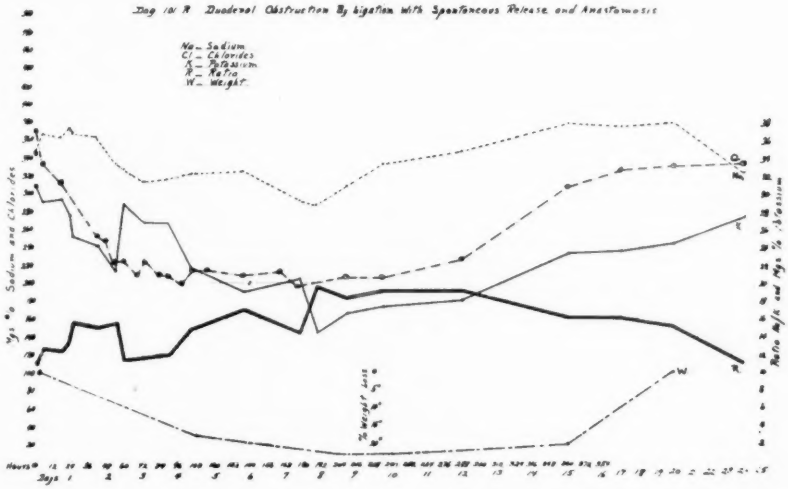


Fig. 7.—Duodenal obstruction with recovery. After becoming moribund, this animal recovered. The ligature had cut through and an end-to-end anastomosis had been established spontaneously. Note that the serum potassium as well as the sodium and chlorides decreased progressively until the animal began to recover. After taking water on the sixth day, there was a sudden drop to very low levels, presumably the result of dilution. Note that the potassium increased more slowly than sodium and chlorides during recovery.

decreased from a preoperative level of 25 to 20 mg. per cent. (See Fig. 8*A* and *B* and Protocols 6 and 7.)

It should be noted that in these animals in which strangulation was superimposed upon obstruction and in which death occurred early the serum potassium never became elevated above the normal preoperative levels.

DUODENAL FISTULAS

In 2 dogs the duodenum was divided, except for a small bridge of tissue at the mesenteric border, approximately 8 cm. below the ampulla of Vater, and the free margins of both ends were sutured to the skin. Lost through the fistula were not only all of the gastric, biliary, pan-

PROTOCOL 6

DUODENAL STRANGULATION

Dog 102R, female; weight, 5.65 kilo. On July 26, 1937, a loop of duodenum, 20 cm. long and about 10 cm. below the ampulla of Vater, was strangulated by an encircling ligature of tape.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	97.8		398	28.0
6	Vomited several times; weak and listless	96.6	328	436	28.8
18	Dry, cold, almost moribund; scum over eyes; both local and general twitchings	96.0	337	398	28.4
18½	Death: weight, 5 kilo., a loss of 10 per cent of body weight Autopsy: abdomen slightly distended and contained much thick bloody fluid; no peritonitis (no exudate or injection of peritoneum); stomach and duodenum distended and below obstruction bowel collapsed; liver swollen; heart and lungs normal				

creatic, and duodenal secretions, but also all water and food ingested. These animals did not vomit and apparently at no time was there retention of secretions. Also, there was no ante-mortem or post-mortem evidence of any physiologic disturbance other than the loss of secretions and yet these dogs died in less than 64 hours, lost from 18 to 20 per cent of their body weights, and showed higher elevations of serum potassium than did the animals with obstruction. In both dogs the potassium, after a preliminary drop, increased to 39.5 mg.

PROTOCOL 7

DUODENAL STRANGULATION

Dog 202L, male; weight, 5.0 kilo. Aug. 3, 1937, a 12 cm. loop of duodenum was strangulated with a broad band of tape, the proximal end being 5 cm. distal to the ampulla of Vater.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	101.0	334	331	25.2
7	Vomited several times; slightly listless	100.2	330	382	20.6
13	Same	99.0	345	361	21.2
16	Less vomiting; weaker	100.8	326	366	22.0
20	Dry, eyes covered with scum	100.6	324	330	20.1
25	Much weaker; some muscle twitching	102.6	306	339	20.2
28	Refuses to stand, irregular twitchings of muscles	104.8	308	336	21.2
31	Death—Autopsy: much bloody fluid in peritoneal cavity; strangulated loop of bowel black and surrounded by omentum; loop of bowel distended and filled with foul-smelling black bloody fluid; general peritoneal surfaces not inflamed (no peritonitis); stomach and duodenum proximal to obstruction moderately dilated, distal intestines collapsed				

per cent from preoperative levels of 26.8 and 22.2 mg. per cent. The chlorides decreased progressively to very low levels as in the ob-

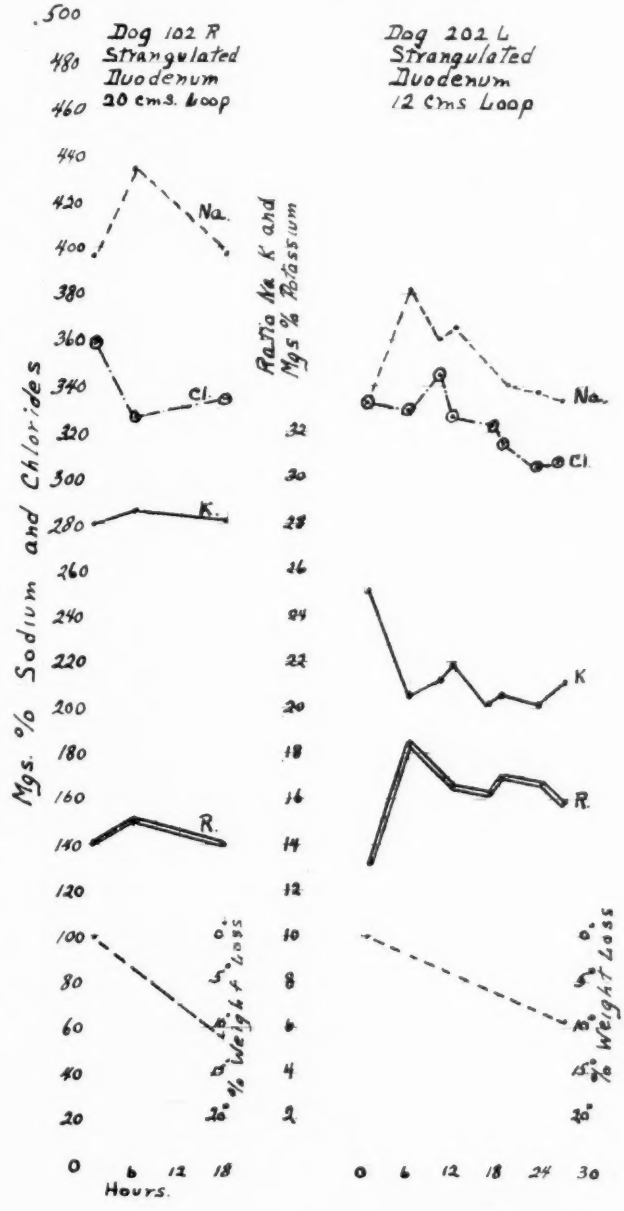


Fig. 8A and *B*.—Duodenal obstruction with strangulation. Despite profound toxemia with early death, there developed no appreciable alterations in the levels of either sodium, potassium or chlorides.

structed animals, and sodium showed no consistent or significant change. The sodium-potassium ratios roughly followed inversely the fluctuations of potassium. See Fig. 9A and *B* and Protocols 8 and 9.

PROTOCOL 8

DUODENAL FISTULA

Dog 104R1, male; weight, 6.46 kilo. July 26, 1937, the duodenum, approximately 5 cm. below the ampulla of Vater, was divided except for a small connecting bridge at the mesenteric border. The edges of the free ends were sutured to the skin.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	100.8		332	26.8
6	Fistulas discharging clear fluid; normally active	102.0	327	357	23.2
18	Some skin irritation; drinks water, looks well	102.4	317	357	26.4
21	Copious drainage; condition good			356	22.2
26	No change	102.6		366	25.2
42	Dry, weaker, scum over eyes; skin digested	102.0		303	29.0
50	Much weaker; twitches slightly	101.1	247	352	39.6
60	Gaunt, refuses to get up; local and general twitchings	100.1	209	316	31.6
62	Death—Autopsy: weight, 5.26 kilo., a loss of 18 per cent of body weight; tissues were dry, the skin around fistulas digested, peritoneal cavity normal, the stomach and bowel collapsed, the right lung hemorrhagic, the left lung and the heart normal				

PROTOCOL 9

DUODENAL FISTULA

Dog 203R, male; weight, 6.1 kilo. Aug. 3, 1937, the duodenum was divided 7 cm. distal to the ampulla of Vater and the edges of both ends were sutured to the skin.

HOURS POSTOPERATIVELY	REMARKS	RECTAL TEMPERATURE	SERUM CHLORIDES	SERUM SODIUM	SERUM POTASSIUM
	Preoperative	101.0	336	376	23.2
6	Drainage of some clear fluid from fistula; appears well	100.4	312	356	22.4
18	Copious discharge from fistula; takes water; appears weak	103.2	281	340	18.2
30	Irritation and beginning digestion of skin about fistula; weaker	102.4	269	336	26.8
34	Same	101.9	263	347	25.6
40	Skin about fistula raw; dry, eye scum; standing is an effort	100.8	248	345	29.6
46	Irregular twitching of muscle groups and generalized trembling	101.0	248	356	33.8
50	Cold, moribund	104.4	254	321	39.6
50½	Death—Autopsy: weight, 4.9 kilo., a loss of nearly 20 per cent of body weight; tissues dry; no peritonitis; stomach and bowel collapsed; both lungs contained large hemorrhagic areas; heart normal				

DISCUSSION

In common with corticoadrenal deficiency states, the conditions which have been the subjects of this investigation, traumatic shock, the shock of hyperpyrexia, high intestinal obstruction, and duodenal fistulas are characterized by profound prostration and by the amelioration of the prostration by the administration of sodium chlorides either alone or with water. This suggested the possibility of a com-

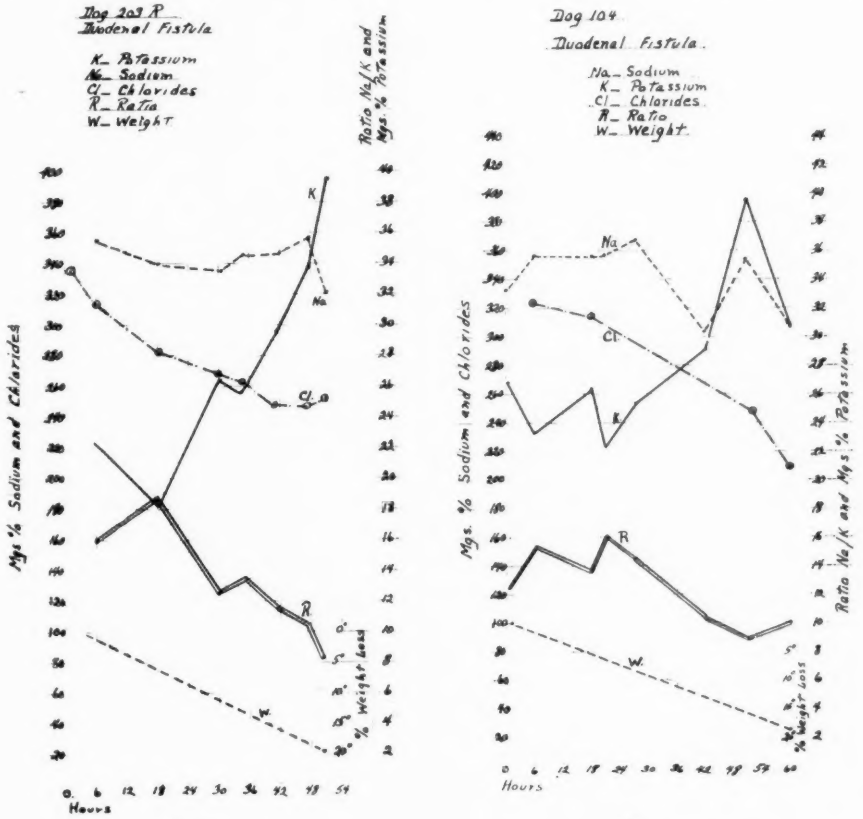


Fig. 9*A* and *B*.—Duodenal fistulas. The duodenum was divided and both ends sutured to the skin so that all ingested food and fluids and all secretions proximal to the level of division were lost through the fistulas. Note the big decrease in chlorides and increase in potassium.

mon biochemical factor. Kendall has shown that in corticoadrenal deficiency states there exists an abnormal ratio between the sodium and potassium of the blood, a relative decrease of sodium and increase of potassium.

Because the ratio of sodium to potassium showed no constant or significant alteration in our experimental animals, it would appear that this factor contributed little or nothing to the production of the abnormal manifestations and death.

In the animals subjected to a progressive, lethal hyperpyrexia, there developed constantly a slight, relative increase of potassium without alteration of sodium. The failure to lose sodium and chlorides as occurs in man can be explained by the fact that the dog has no sweat glands. Therefore, the biochemical changes which take place under these circumstances are not comparable in the two species.

In an investigation of high intestinal obstruction in cats, Scudder, Zwemer, and Truszkowski constantly found an elevation of potassium in whole blood and stated that the potassium accumulated in sufficient concentration in the blood to produce lethal potassium poisoning. They suggest that potassium is the toxic factor which produces symptoms and death in high intestinal obstruction.

In striking variance with their results are the results of our experiments. True, potassium did become elevated considerably above the preoperative levels in approximately one-half of the obstructed animals in our series, but, if potassium is the toxic factor, it should become elevated in all instances of obstruction with toxemia. In 2 dogs which became moribund and then recovered, the potassium never became elevated above the normal preoperative levels. Likewise, in the two dogs with strangulated loops of bowel in which the toxemia was most profound and death occurred very early, the potassium never became elevated above the normal preoperative levels. It is also of interest that the highest rises of potassium occurred in the two dogs with duodenal fistulas. In these animals there was no obstruction, merely a total loss of fluids and their solutes. They did not vomit and were able to take fluids. They lived longer than the obstructed animals but died with the same clinical manifestations. Also, with one exception, they showed greater weight losses than the obstructed dogs.

The discrepancy between our findings and those obtained by Scudder and others may be explained by the difference in species of animals used or by the fact that their determinations were made upon whole blood and ours upon blood serum. To determine this point, analyses of sodium and potassium were made upon both serum and whole blood drawn simultaneously from one obstructed dog. The results were in no way comparable. As shown in Fig. 6*B*, there was much less sodium in whole blood than in serum and with obstruction the potassium in whole blood increased slightly while that in serum decreased greatly. Consequently, if the toxicity of a substance depends upon its concentration in serum it cannot be assayed in the dog by determinations made upon whole blood.

Of interest was the relative duration of life; this in order from longest duration is as follows: those with fistulas, 64 hours; pyloric obstruction, 52 hours; duodenal obstruction, 42 hours; strangulated short duodenal loop, 27 hours; and strangulated long duodenal loop,

18 hours. Consistent with other observers, the duration of life in animals with strangulated loops of bowel is inversely proportional to the length of the loops.

CONCLUSIONS

1. Both adrenalin and inhaled ether caused precipitous but transient drops in serum potassium but no appreciable change in serum sodium and chlorides.

2. In traumatic shock there was no consistent alteration of serum sodium, potassium, or chlorides.

3. Hyperthermic shock was associated with a marked rise of serum potassium, rising to levels of 30 to 50 per cent above the normal preoperative levels. Serum sodium and chlorides unchanged. Consequently the sodium-potassium ratios varied inversely with the potassium. As the dogs have no sweat glands, there is no loss of fluids or salt through the skin as occurs in man. This, no doubt, accounts for the difference in the response of sodium and chlorides to hyperpyrexia in the two species.

4. In high intestinal obstruction there was no consistent change in serum potassium or sodium, but there was, except in one instance, a large fall in chlorides. There was no evidence in our experiments that potassium contributed to the production of symptoms and of death in high intestinal obstruction or in duodenal fistulas.

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THE SURVIVAL OF CLOSTRIDIUM SPOROGENES, BACILLUS SUBTILIS, AND STAPHYLOCOCCUS ALBUS ON SURGICAL (CATGUT) LIGATURES

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THE adoption of more rigid and uniform procedures for the sterility testing of surgical ligatures has raised the question of the ability of different types of bacteria to survive on ligatures. The necessary handling of ligatures during the sterility test involves a risk of occasional contamination, and it therefore becomes important to know whether a particular type could have been present on the ligature or may have been introduced through errors in technique.

Consideration of this problem led us to the conclusion that, irrespective of the sterilizing process to which the ligature has been subjected, an organism cultured at the time of the sterility test in order to be significant of contamination must be capable of remaining viable in the fluid in which the ligature is stored. The storing fluids used by manufacturers differ greatly. However, they may in general be classified in two groups of chemical compounds: the aliphatic alcohols used as storing fluids for nonboilable ligatures, and benzene and related compounds used for boilable ligatures. Since the collagen of the ligature is chemically altered in aqueous media and the ligature must, therefore, be subjected to a process of dehydration during manufacture, it appeared to us that bacteria present on them must also be dehydrated, and that viable organisms encountered in the sterility test must have survived in this state in order to have been present on the ligature. The usual figures given for the resistance of aqueous suspensions of bacteria to chemical agents could not be directly applied in this case, due to the difference in suspending medium.

We have determined the resistance of *B. subtilis*, *Cl. sporogenes*, and *Staph. albus*, when dried on ligatures, to denatured alcohol and toluol. These organisms were selected as representative of aerobic and anaerobic sporulating rods and nonsporulating organisms respectively. They also represent types encountered in the culture of ligatures. Alcohol and toluol were chosen as representative of the two main classes of storing fluids in common use.

MATERIALS AND METHODS

Ligatures.—Heat-sterilized ligatures for these experiments were obtained from the laboratories of Armour and Company. These were

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packed without storing fluid. Size No. 2, both plain and chromic, was used throughout. The ligatures were washed in water for twenty-four hours and transferred to the suspensions of bacteria (described below). After incubation in the suspensions, the ligatures were removed to sterile tubes and desiccated over $CaCl_2$ at reduced pressure in the ice-box. The time of desiccation varied from one to three weeks.

Suspensions of Organisms.—The *Cl. sporogenes* and *B. subtilis* were stock strains from this laboratory. The *Staph. albus* culture was encountered during the sterility test. Aerobic organisms were grown on nutrient agar in Kolle flasks and the growth washed off with sterile water. Anaerobic cultures were grown in beef-heart medium, the growth collected by centrifugation and resuspended in sterile water. Incubation of cultures was sufficiently long to ensure good growth and spore formation by those organisms which produced spores. When viable counts were made of the suspensions prepared by this method, the agar plate method was used.

Storing Fluids.—Ninety-five per cent alcohol (ethyl alcohol denatured with 5 per cent methyl alcohol) was sterilized by Berkefeld filtration. Toluol was sterilized by heat. These fluids were added to the tubes containing the desiccated ligatures, care being taken to ensure that organisms did not survive on the sides of the tubes above the level of the fluid. Tubes kept for long time intervals were sealed.

Experimentally contaminated ligatures subjected to heating were treated at sterilizing temperatures in the absence of water.

After exposure to the test conditions, the ligatures were cultured by the method of Meleney and Chatfield.[1] Bacteriological tests were made to determine the identity of the organisms cultured.

RESULTS

None of the organisms survived heating in the dehydrated state. Ten ligatures contaminated with each of the test organisms were treated in this manner. The organisms, therefore, apparently acquired no unusual resistance to heat sterilization by the dehydration process.

In a preliminary experiment it was found that the sporulating organisms, *B. subtilis* and *Cl. sporogenes,* could survive exposure to both alcohol and toluol for at least seventeen days. In later experiments, Table I, *B. subtilis* survived in each of these solutions for six months. *Cl. sporogenes* survived well in alcohol for fifty-six days, and growth was obtained from one of nine ligatures tested after six months. It therefore appeared doubtful that the strain under consideration would have been viable after a much longer period of exposure. In toluol growth of *Cl. sporogenes* was obtained only from three of five ligatures tested at fifty-six days, all the other cultures being negative in the later experiments. In view of the results of the earlier experiments these are somewhat difficult to interpret. In view of the inconsistency of the

TABLE I

SURVIVAL OF ORGANISMS IN TOLUOL AND ALCOHOL WHEN DRIED ON LIGATURES

CULTURE	TIME EXPOSED	TEST SOLUTION				CONTROLS	
		ALCOHOL		TOLUOL			
LIGATURES		TESTED	GROWTH	TESTED	GROWTH	TESTED	GROWTH
Cl. sporogenes	7 days	5	5	5	0	2	2
	14 days	5	2	5	0	3	0
	21 days	5	5	5	0	3	3
	28 days	5	3	5	0	3	3
	56 days	5	5	5	3	2	2
	6 mo.	9	1	10	0	5	5
	Total	34	21	35	3	18	15
B. subtilis	7 days	4	4	5	5	4	4
	14 days	5	5	5	5	4	4
	21 days	5	5	5	5	3	3
	28 days	5	5	5	5	3	3
	92 days	5	5	5	5	3	3
	6 mo.	10	10	7	7	7	7
	Total	34	34	32	32	24	24
Staph. albus	5 min.	10	10	22	0		
	10 min.	10	10	22	0		
	15 min.	10	10	22	0		
	20 min.	10*	10	22	0	32	13
	Total	40	40	88	0	32	13

*Ligatures were tested at intervals up to twenty-four hours without obtaining further growth.

positive result obtained at fifty-six days in the toluol series of "sporogenes" ligatures, it would seem that this positive culture was due to some technical error. We do not mean to imply, however, that any sporulating organism encountered during the routine examination of ligatures for sterility should be disregarded. The results as a whole nullify such an implication, and we feel that the observation that *Cl. sporogenes* does not show the same capacity for surviving under the conditions of these experiments as does *B. subtilis* has no practical bearing on the present problem.

Staphylococci were found to survive very poorly the drying conditions of these experiments. Despite the fact that suspensions of approximately 1×10^{13} viable organisms per cubic centimeter were used to contaminate the ligatures, they were found to be sterile upon removal from the desiccator in several experiments. In preliminary experiments with these organisms both moist and dehydrated ligatures were used. The former were found to be sterile after exposure for ten minutes, and the latter after exposure for fifteen minutes to both toluol and alcohol. These were the shortest time intervals tested in this experiment. The results of later experiments are given in Table I. It is apparent from the results of these experiments that this organism could not survive exposure to the test solutions.

Whether the ligatures were chromic or plain did not affect the results of these experiments.

CONCLUSIONS

B. subtilis when dried on surgical ligatures was found to survive exposure to either toluol or alcohol for at least six months.

Cl. sporogenes survived in alcohol for six months, but showed only slight resistance to the action of toluol.

The experiments in general, however, indicate that any sporulating organism encountered in the routine sterility test might have been present on the ligature and should be considered as significant of possible contamination of the ligature, unless resampling indicates that they are sterile.

Staph. albus did not survive exposure to either toluol or alcohol for sufficiently long periods of time to be of significance to the contamination of ligatures, and on the basis of these experiments we feel that, when encountered in the routine sterility test, it indicates error in technique rather than contamination of the ligature.

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TREATMENT OF THE UNDESCENDED TESTIS: WITH SPECIAL REFERENCE TO THERAPY WITH HORMONES*

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UNDESCENDED testis is one of the more common genitourinary anomalies with which the surgeon must deal. It occurs in from 0.1 per cent (Marshall) to 0.12 per cent (Monod and Terrillon) of males. The statistics of the Austrian army show that 2.2 cases of undescended testis occurred in every 1,000 men drafted for military service (Ziebert). According to the War Department's medical records with the World War, there were 3.1 cases of ectopy for every thousand men examined. Eccles found 2 per cent of undescended testes in 48,000 hernias. Bevan, Coley, and Wangensteen put the incidence of retained gonad at 1 in 500 men.

Incomplete descent is more common on the right than on the left side. From the statistics of Berger, Hofstatter, and others, the incidence of right-sided maldescent is equal to that of double and left-sided retention combined. In 20 per cent of undescended testes the deformity is bilateral (Wangensteen).

Pain, torsion, hernia, and malignancy are the most common complications of undescended testis. However, except for hernia, most patients with undescended testis do not present themselves for treatment because of complications. Some are conscious of the aberrant position of the ectopic gland. Others are concerned about the fertility of the retained gonad. Not a few, wishing to avoid a surgical operation, ask about the chance of spontaneous descent or the results of "injection" (endocrine) therapy.

The surgeon is confronted with the problem of selecting the best treatment for these patients. If the treatment is to be surgical, should the retained testis be removed, because of the danger of malignancy or because of its questionable function, or should it be scrotally fixed? If the testis is anchored in the scrotum, is the result to be considered purely cosmetic or will the function of the organ be improved? Although orchiopexy has been performed for more than a century, it is surprising how few investigators have inquired if the undescended gonad had any function, or, if such a function existed, whether it could be maintained or improved by scrotal fixation. From a review of the literature, it seems established that in most cases the undescended

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testis may have an internal secretion and occasionally may possess an external secretion sufficient for potential, if not absolute, fertility. It is estimated that 10 per cent of untreated human cryptorchids remain fertile (Uffreduzzi). It has been proved clinically that as high as 82 per cent of patients treated by orchiopexy have active spermatozoa in the semen (MacCollum). Placing the slightly atrophic or immature retained testis of man and the pig in the scrotum has been shown experimentally to allow a mature germinal epithelium to be produced (Wangensteen). The degree of maturity after scrotal fixation is never as great as that seen in the case of the experimentally produced cryptorchid so treated. However, clinically and experimentally the value of scrotal fixation for testicular development has been proved beyond doubt.

There is a diversity of opinion among surgeons as to the best treatment for the undescended testis. Some believe that the ectopic gland is potentially malignant and should be removed. Others believe that, if left alone, most of these retained gonads will descend spontaneously. Recently the reports of some investigators indicated that the results from hormonal therapy are equally as good as, if not superior to, those obtained by surgical treatment (orchiopexy). In formulating a rational plan of treatment of the undescended testis, one is influenced by the number and type of cases he has seen, his surgical experience and that of his associates, and the type of case that receives hormonal therapy.

The questions of malignancy of the testis, spontaneous testicular descent, and surgical technique are beyond the scope of this paper and are discussed in detail elsewhere. In review, however, it may be said that the undescended testis should not be considered a precancerous lesion, as only about 2 per cent of such organs develop tumors (Hinman). Spontaneous descent is a rare occurrence in our experience; the policy of "watchful expectancy" after puberty is not justified, knowing from experimental studies how atrophic the ectopic testis becomes when deprived of its scrotal environment. Wangensteen has described a modification of the Keetley-Torek operation which has given uniformly good results in the surgical treatment of this condition. The only change in technique of the operation since its initial description has been the substitution of silk for catgut sutures in performing the scrotal-crural anastamosis and the hernial repair.

For the past four years, at the University of Minnesota Hospitals, some cases of undescended testis have been treated by hormones. Schapiro in 1930 reported genital growth and testicular descent by anterior pituitary-like substance in boys and young men with hypogenitalism and cryptorchidism. Since then there have been several series in the literature of undescended testis treated by this material. Thomp-

son and others and Cramer recently have summarized the results of most investigators; in over 70 per cent of cases descent of the retained gonad has occurred. How critically some of the cases were observed may be questioned when in one series the testis was reported to have descended within three hours after treatment (Harris). About one-half of the cases showed signs of hypopituitarism of adipogenitodystrophies and received other therapy besides pituitary extract (thyroid extracts, diet, etc.). From a summary of published data, the original position of the gonad successfully brought into the scrotum by anterior pituitary-like substance was as follows: upper scrotum, intra-abdominal, and inguinal in the order named (Thompson and others).

Kunstadter, Robins, Schapiro, and Goldman and Stern believe that the administration of extracts of pregnancy urine is indicated in hypopituitarism of the male characterized by genital underdevelopment. However, the clinical diagnosis of pituitary or other endocrine dyscrasia always is subject to considerable variation in interpretation. Hess, Kunstadter, and Saphir believe that, if cases of cryptorchidism could be studied with more objective criteria, a more rational therapy could be instituted. It is known that whenever gonadal function is diminished or absent, as in adult hypogonadism, the menopause, or castration (Evans, Engle, and Smith), there is an excessive excretion of the gonadotropic hormone, presumably of pituitary origin. Katzman and Doisy have shown that the urine of normal children contains little or no gonadotropic hormone. Hess and co-workers reasoned that, since in the castrated person or in cryptorchid boys the gonadotropic hormone is presumably of pituitary origin, it seemed logical to conclude that the presence of gonadotropic substance in the urine of cryptorchids indicates an active anterior pituitary gland as to gonadotropic function. The appearance of the hormone in the urine may be due to insufficient activity of the gonad which failed to modify the hormone or remove it from the blood. On the other hand, the occurrence of cryptorchidism with an absence of gonadotropic hormone from the urine may be interpreted to mean either the presence of a primary pituitary dysfunction or the presence of a functionally active bilateral undescended testis, or at least one functionally active testis.

Accordingly Hess and others determined in a semiquantitative manner the excretion of gonadotropic substance in the urine of cryptorchid boys before and after treatment with gonadotropic substance. Nine of thirteen of their cases of cryptorchidism responded to the use of anterior pituitary-like factor by descent of the testis and disappearance of the hormone from the urine. They believe that, in the absence of mechanical obstruction to descent, the best results after using anterior pituitary-like substance are obtained in those cases of undescended testis that have gonadotropic hormone in the urine which disappears after treatment.

Hardy, Bigler, and Scott have reported one of the largest series to date of cryptorchids treated by hormonal therapy. In one group 32 boys with 40 undescended testes were treated with gonadotropic principle of the anterior pituitary gland. In 26 cases the testicles remained unchanged in location; in 4 there was partial descent and in 10, or 25 per cent, there was complete descent. After discontinuing treatment, however, only 7, or 18 per cent, remained descended. In another group antuitrin-S* was used in the treatment of 23 patients with 31 undescended testicles. No change was observed in 12 testicles; 4 descended partially, and 15, or 48 per cent, descended completely. However, only 14, or 45 per cent, remained descended upon further observation. Both extracts were used in the treatment of 16 boys with 20 undescended testicles, and in 9, or 45 per cent, there was complete descent, which was permanent in 5, or 25 per cent, of the cases. They found that descent of the testicle usually begins to take place before 4,000 rat units of gonadotropic substance have been given.

Undoubtedly, in the literature more prominence has been given to the successes than the failures. Few contraindications to therapy with gonadotropic hormones are recognized and the method is too recent to permit investigation into the possibility of late complications. Thompson, Bevan, and others, obtained descent in 4 inguinally retained testes in 21 instances of cryptorchidism (19 per cent). Mimpress, who obtained descent in only 6 of 20 cases of undescended testis so treated, believes that anterior pituitary-like substance should be used chiefly in bilateral cryptorchids with subnormal genital development. Cabot has referred to the possibility of late atrophy of the testes and Cole has produced atrophy of the tubules of the testes by high doses. Goldman and Stern have commented on the possible development of precocious sexual maturity, and for this reason consider 9 years as the earliest age at which treatment with gonadotropic hormones should be started. In this clinic also there is some hesitancy in using anterior pituitary-like substance in very young children, but Dorff and Aberle and Jenkins have used this hormone in children about 3 years of age with no untoward results. Geschickter and others found that extracts of the urine of pregnancy in young male monkeys produced hypertrophy of the prostate and enlargement of the breasts. However, from a survey of the available literature and the experience at this clinic, the danger of most of the above complications would seem more theoretical than real.

THE UNIVERSITY OF MINNESOTA HOSPITAL SERIES

The results at the University of Minnesota Hospitals using anterior pituitary-like substances in the treatment of retained testis are summarized below. Four products have been tried: antuitrin-S (Parke-

*Anterior pituitary-like substance from pregnancy urine (Parke-Davis).

Davis), follutein (Squibb), prephysin (Chappell), and A. P. L. (Ayerst). The last three products have been used in only a few cases.

A. *Antuitrin-S.*—It has been our practice to inject 1 c.c. (100 rat units) of antuitrin-S daily into the subcutaneous tissue of the thighs for thirty days (3,000 units). If no results are obtained before this time, the patient is then observed every month for three months and then every three months. Some of the cases in which no results were obtained have been followed for two years.

Thirty patients with 36 undescended testes have been treated to date with antuitrin-S (Parke-Davis) in this clinic. The ages of the patients varied from 4 to 24 years. The testes were bilaterally retained in 6 instances. Two of the bilateral cryptorchids also had hypospadias and there was a suggestion of Fröhlich's syndrome in 1 bilateral and 1 inguinally retained case. Five patients responded to the treatment by degrees of descent of the testis into the scrotum. While descent of the retained gonad was complete in 3 cases, it was only to a high scrotal position in the other 2 cases (U. H. No. 648741 and No. 630358). Both of these patients were older and later submitted to orchiopexy. One of these patients (U. H. No. 648741) received a total of 6,000 units over a period of two months. It is interesting that no spermatozoa were seen in either the biopsy or smear of the testis when the patient later submitted to orchiopexy. Also the microscopic section of the testis showed the usual atrophic appearance (HO-37-574).

No untoward results have ever been observed over a period of two years following the use of antuitrin-S in this clinic. There was suprapubic edema in 3 cases which disappeared after treatment and 1 patient complained of swelling in the left breast which clinically was thought to be a fibrous mastitis. In none of the cases was there a demonstrable increase in the size of the penis. The testes of the successfully treated cases often enlarged; we could not be sure that there was any change in size of the testes in the unsuccessfully treated cases. The scrotum of one boy (see chart, U. H. No. 694590) became red and slightly edematous after 2,000 units of antuitrin-S had been administered. In none of the cases was there premature appearance or increase in the amount of pubic, axillary, or facial hair. Five patients noticed increased frequency of erections.

B. *Follutein.*—Two patients, aged 21 and 23 years, were treated by follutein (Squibb) for undescended testes. The testes were bilaterally retained (inguinal) in 1 case, and inguinally arrested on the right side in the other. One cubic centimeter of follutein (125 c.c.) was injected daily for 10 days into the subcutaneous tissue of the thigh (1,250 units). No improvement was noted following this therapy; the patients were observed for a period of one year.

C. *Prephysin.*—Three patients, aged 2, 7, and 11 years, were treated with prephysin (Chappell). The undescended testes were unilateral and inguinally retained in all 3 cases. The 2 younger boys were brothers. Prephysin contains the follicle-stimulating principle of the pituitary gland, including small amounts of luteinizing factor. It differs from antuitrin-S and follutein in that it is extracted from the pituitary gland itself and not from pregnancy urine as the latter two are. One-half of one cubic centimeter of prephysin (1 c.c. is equivalent to 25 units) was injected daily for four days into the subcutaneous tissue of the thighs of these 3 boys. No descent of the testis was observed in any of these cases over a period of nine months.

D. *A. P. L. (Anterior Pituitary-Like Substance) (Ayerst).*—Four patients have been treated to date with this hormone, which is extracted from placental tissue. The special strength solution, 500 units per cubic centimeter, has been used in doses of ½ c.c. every other day until fifteen injections have been given. Three patients with unilateral, inguinal testes have been treated with this substance and observed less than five months. No beneficial results have been noted to date. However, in the fourth patient, a boy 9 years old, with bilateral inguinal testes, complete descent of both testes occurred after the ninth injection.

Thus, in summary, of 36 patients with undescended testes who were treated by gonadotropic substances and followed six months or longer, degrees of descent were noted in 6 (16 per cent). In 4 descent was complete. It is possible that the dosage and period of injection of anterior pituitary-like substances in these cases were not adequate, but these factors are comparable to those reported in the successfully treated cases in the literature (Hardy, Bigler and Scott, Cramer).

AN EVALUATION OF THE TREATMENT OF ECTOPIC TESTIS BY GONADOTROPIC SUBSTANCE

Rubinstein has summarized the current concept regarding hormonal therapy in the treatment of undescended testis in the following statement: "The water-soluble fraction of pregnancy urine seems to produce testicular descent only if the pituitary gland is sexually underdeveloped. It then leads predominately to a stimulation of the interstitial cells of the testicle and may result in descent when a mechanical block does not exist."

In the cases of cryptorchidism which have been operated upon at the University of Minnesota Hospitals, nearly all have shown evidence of mechanical causes for arrest of descent. The testis was often lodged in pockets or bound down by adhesions to such extent that it was with great difficulty that they were freed or the spermatic cord lengthened sufficiently by loosening adhesions. It is almost inconceivable how one could bring such testes into the scrotum without surgical measures.

MacCollum thinks that it is incongruous to suppose that at some time this fibrous tissue will disappear and allow the testicle "to drop like a plummet" into the scrotum. In our series 5 patients with undescended testes who had been treated with antuitrin-S (total 3,000 units in each except 1 case that received 6,000 units), submitted to operation three to six months later. The same degree of fibrous adhesions and mechanical arrest seemed to be present in these as in cases which had not been treated by gonadotropic substance prior to operation. The mechanical obstruction to spontaneous or induced testicular descent as revealed by operation seems adequate explanation of failure of hormonal therapy.

One wonders if many of the successful results with endocrines reported in the literature were not obtained in cases of physiologic ectopy and not true undescended testes. By physiologic ectopy is meant the condition in which one finds a normally descended testis with a very active cremaster which pulls the gonad into a high scrotal, inguinal, or even abdominal position. This condition, also called ectopy en retour, has been little appreciated by most investigators. The factor at fault in this anomaly is the hyperactive cremaster (physiologic), while that in the case of the true undescended testis is the failure of complete descent (anatomic). Some instances of spontaneous descent of incompletely descended testes are undoubtedly cases of physiologic ectopy. It may be that anterior pituitary-like substance is valuable in the treatment of physiologic ectopy, but it should be remembered that such cases often descend spontaneously. It is not to be inferred that the writer believes that all of the reported cases of retained testes that have descended after a course of hormonal therapy are cases of physiologic ectopy. However, because of the results obtained with this therapy at this clinic, and because of the existence of mechanical causes for testicular arrest in most of the operated cases, it is believed that endocrine imbalance *alone* does not fully explain the cause or give a rational basis for treatment in *all* cases of true testicular maldescent.

There can be no doubt that in some cases of cryptorchidism gonadotropic hormones will cause descent of the testis into the scrotum; in others endocrine therapy is of no value and only surgery will remedy the aberrant position of the gonad. In a third group testicular descent or size may be enhanced by the pre- or postoperative use of glandular substances. Just what percentages of undescended testes fall in the above classifications are unknown. However, a method that gives the patient any chance of avoiding a surgical operation certainly merits trial; hence, the use of hormonal therapy, at least a preliminary form of treatment, seems indicated.

A SUGGESTED PLAN OF TREATMENT FOR THE UNDESCENDED TESTIS

It is known from the experiments of Moore and Wangensteen that the testis must be in the scrotum before spermatogenesis occurs or de-

generative changes will set in. Puberty in the male lies between the ages of 13 and 15 years, without regard to race, climate, or individual differences (Spangaro), the extremes being 9 years (Scammon) and 18 years (Crampton). Therefore, treatment of the congenitally retained gland may be deferred until the patient is 9 to 11 years old. If surgery is contemplated, there is no objection to operating upon a patient with uncomplicated retained testis at any earlier age, but it is unnecessary. The presence of a large associated hernia may necessitate earlier surgical intervention. The presence of an undescended testis precludes the use of a truss and the injection of sclerosing solution in the treatment of inguinal hernia. It is our practice at the University of Minnesota Hospitals to suggest first a trial of anterior pituitary-like substance in all uncomplicated cases of undescended testes before surgical procedures. Possibly the determination of gonadotropic hormone in the urine before treatment (Hess and others) will aid in the selection of these patients. It would be of practical value to know before treatment if there existed mechanical causes for the testicular maldescent, but unfortunately no way to determine this is known to date. There are various methods of administering hormonal therapy. While the available gonadotropic substances are well standardized, the dosages and interval of injection prescribed by various authors are rather empirical. At this clinic, the methods of treatment outlined above are still followed, except that greater dosages are given in some instances, as well as subsequent courses of injections, at two- to three-month intervals, if the patient is under 9 years of age. We have had no experience with extremely high dosages of gonadotropic hormones in the treatment of cryptorchids at this clinic as the cost is prohibitive. If, after six months of observation, no results have been observed with hormonal therapy, surgical treatment of the undescended testis is advised if the patient is 9 years or older.

SUMMARY

Treatment of the retained gonad may be deferred until the patient is 9 to 11 years old. With the hope that the case may be a favorable one, a course of treatment with pituitary-like substance may be tried first in cryptorchids before surgical procedures. Reports in the literature of cryptorchids treated by gonadotropic hormones reveal that in as high as 70 per cent of the cases there is descent of the testis into the scrotum. This form of therapy has been less efficacious in the cases treated to date at this clinic, degrees of descent being obtained in only 16 per cent of the cases so treated. No untoward effects resulting from hormonal therapy have been observed.

For reasons mentioned elsewhere, it is believed that endocrine imbalance *alone* does not fully explain the cause or give a rational basis for treatment in *all* cases of true testicular maldescent. However,

gonadotropic substance should be given at least a preliminary trial in the treatment of undescended testis, and, if no results are obtained, an orchiopexy should be performed.

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PRIMARY RETROPERITONEAL TUMORS

Report of Three Cases and One Hundred Seven Cases From the Literature

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THE present report is based upon two cases of primary solid retroperitoneal tumors and one retroperitoneal cyst unconnected in origin with any of the abdominal viscera. For reasons which will appear obvious, these three patients were subjected to different methods of treatment—the one to radiotherapy, the other two to operation.

Primary retroperitoneal tumors are not of frequent occurrence. They present unusual difficulties in diagnosis, operative intervention, and prognosis; in prognosis, because even the nonmalignant types are prone to recur, especially lipomas.

In previous communications I have described a neurogenic retroperitoneal growth (Schwannoma[27]), as well as three tumor masses encountered retroperitoneally in the pelvis, which presented diagnostic problems.[28] The present discussion is limited to primary growths not arising from abdominal organs (liver, pancreas, adrenals, intestines, genital or urinary organs). Likewise, because the diagnostic problems and operative techniques are different, mesenteric and omental growths, although extraperitoneal, are not included. The few neoplasms described as specifically arising from residual urogenital embryonic rests also are not considered (Hansmann and Budd[56]).

CASE REPORTS

Case 1.—Gynecological Service, The Mount Sinai Hospital, A. M., female, aged 8½ years. The child had complained of fatigue and loss of weight for the last six months (loss of twenty-eight pounds in six months). Acute symptoms four weeks in duration. A slender child in the last degrees of emaciation; weight, forty pounds. In marked contrast to the state of nutrition was a greatly distended abdomen. Almost the entire abdomen was occupied by a firm yet apparently fluctuating mass arising from the left flank. Tympany was limited to a narrow zone along the right flank and epigastrium (Fig. 1). Rectal examination showed the Douglas free although pressed upon by the mass. A small uterus could be felt. X-rays of the chest were negative. Gastrointestinal x-ray showed the stomach compressed upward, the transverse and descending colon displaced to the right and backward. The abdomen showed a large homogeneous shadow (Fig. 2). The circumference of the abdomen at the umbilicus was 69 cm. The superficial abdominal veins were greatly distended.

The condition was considered inoperable, but exploration was decided upon. Operation, Nov. 21, 1929. Upon opening the abdomen, I found a large semifluctuant

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mass of the size shown in the diagram (Fig. 1) which I diagnosed as teratoma. The mass covered the entire posterior surface of the abdomen and had bulged into the mesentery of the small intestine as well as that of the mesosigmoid and descending colon, separating the leaves of the mesenteries and advancing to within 1 cm. of such portion of the small intestine as could be visualized. The intestine appeared secondarily adherent to the mass. The surface of the tumor beneath the posterior abdominal peritoneum was extremely friable and vascular. It burst during the examination, profuse hemorrhage ensuing. Several areas were taken for biopsy purposes. A Mikulicz drain was inserted, the end of which was drawn through the abdominal incision which was sutured except for passage for the drain.

The child recovered from this intervention, and, in order to give it the only possible chance, at first a radium pack was applied, Dec. 5, 1929, 10,000 mg. hours,

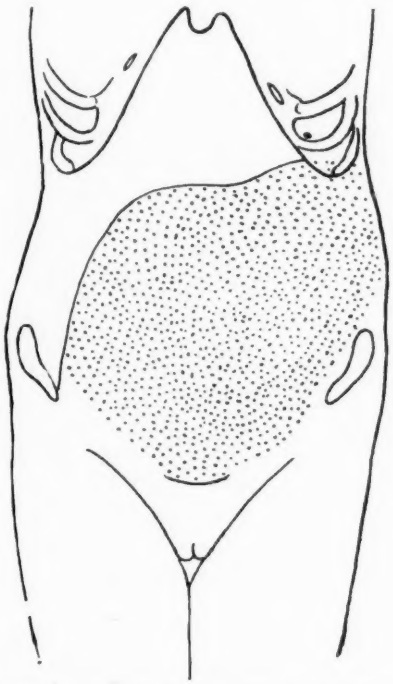

Fig. 1.—Case 1. Schematic outline of extent of tumor.

over fields of 6 by 8 cm., at a distance of 6 cm., with a filter of 0.1 mm. of platinum and 1 mm. of lead. Between Dec. 13, 1929, and Dec. 18, 1929, five high voltage x-ray exposures were given through the right and left gluteal regions (100 per cent). The child showed distinct improvement, the abdominal distention and mass subsiding. Between Feb. 8, 1930, and March 13, 1930, six treatments of high voltage x-ray were given through the anterior pelvis, right and left gluteal regions, totaling 66 per cent erythema dose. The improvement continued and therefore from May 27, 1930, to June 7, 1930, four more x-ray treatments were given, 60 per cent erythema dose, through the anterior abdomen, and 40 per cent through the right and left gluteal regions. The amount of x-ray given according to the old type of measurement amounted to 200 per cent to the right and left gluteal regions and 135 per cent to the anterior pelvis.

Within a year the child appeared perfectly well. Her abdominal and rectal examinations were normal and throughout the intervening

time she has not only continued to be in perfect health, but has shown normal growth and development. Now at the age of 17 years, eight and one-half years since the exploration, A. M. is a normal, healthy, well-built young woman. She has menstruated four times, September, 1936, May, August, and October, 1937. The genital organs are normal and

Fig. 2.—Case 1. X-ray of abdomen after barium meal. Stomach and small intestine crowded upward; transverse and descending colon pushed to right.

do not appear to have been permanently involuted by the large doses of radium and X-ray given.

The specimen consists of a myxomatous connective tissue which shows in places conspicuous capillary formations. In places there are smooth muscle bundles within the myxomatous tissue. Other areas consist of a very cellular fibroblastic tissue, the fibroblasts having a large pale

nucleus, as in more immature cells. Many fragments of the tumor mass are hemorrhagic and have lost their structure. Undifferentiated mesenchymal neoplasm with angiomatous areas. (Fig. 3.)

CASE 2.—Mrs. L. B., aged 39 years, referred to me Nov. 17, 1936. Para iii, youngest child 8¾ years old. Menstrual history normal. Since four months an

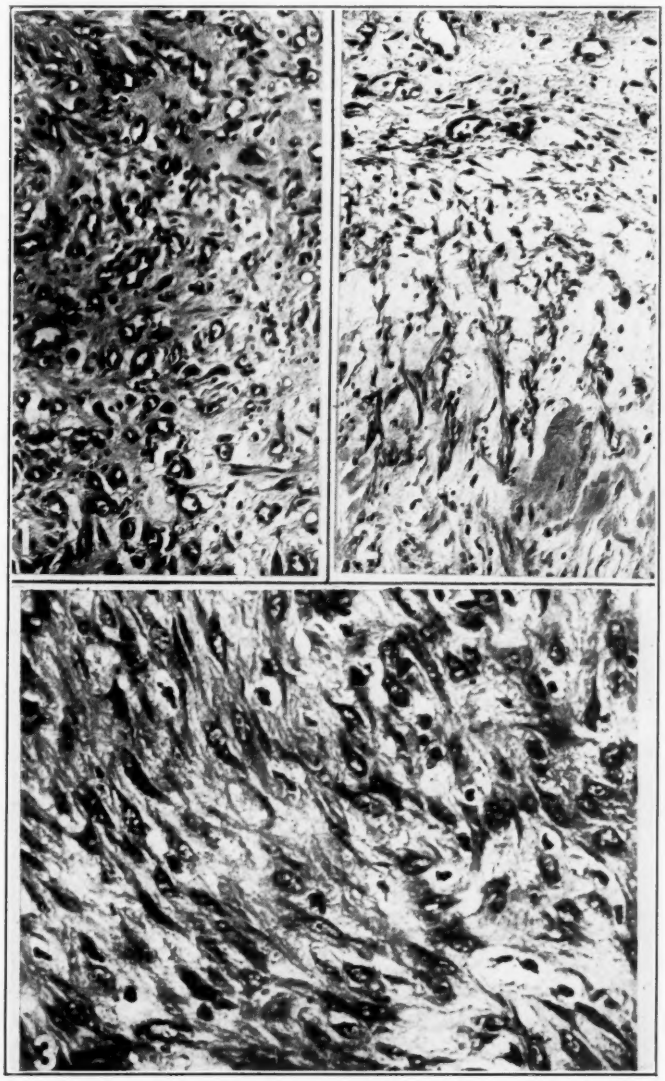

Fig. 3.—Case 1. Three areas (biopsy). Photomicrograph: *1*, angiomatous tissue; *2*, myxomatous tissue and smooth muscle; *3*, embryonal (mesenchymatous) tissue.

increase of the abdomen. Occasional regurgitation of food. Slight constipation and occasional difficulty in starting the urinary stream. Five pounds' loss in weight in three months. Because of the increased size of the abdomen, a pregnancy test had been performed and found negative.

The patient was an essentially normal woman. The abdomen appeared diffusely distended, and a fluctuant mass could be felt reaching to three fingers above the

umbilicus on the right side, lower on the left. Both flanks percussed dull. There was no fluid wave. The inguinal glands were normal. There was a small lipoma in the right buttock.

Pelvic examination: the uterus could not be differentiated from the mass which on the left reached down into the pelvis. The diagnosis was that of ovarian or uterine neoplasm, not malignant as Douglas' cul-de-sac appeared uninvolved.

Operation, Nov. 20, 1936, private pavilion, the Mount Sinai Hospital. A left paramedian suprapubic incision was made. An apparently cystic mass presented. Spread upon its anterior surface was a long horizontally pointing vermiform ap-

Fig. 4.—Case 2. Conditions on opening abdomen. Horizontal appendix; leaves of mesenteriolum and mesentery of small intestine separated by the growth; lower ileum fixed horizontally; mesosigmoid invaded.

pendix, its mesenteriolum separated and spread on the surface of the tumor. The tumor likewise had separated the mesentery of the terminal ilium, rising upward behind the cecum and ascending colon. (Fig. 4.)

The appendix was first freed by incising its mesenteriolum above and below, and then removed. The posterior peritoneal incision was extended vertically downward from the point at which the tip of the appendix had lain. At this stage both ovaries and tubes were found normal, the uterus enlarged by small fibroids to the size of a seven weeks' pregnancy. The posterior peritoneal incision could not be extended upward because the fixed, transversely running ilium was encountered.

Fig. 5.—Case 2. First stage in development of tumor. Appendix removed; tumor freed from between leaves of mesosigmoid.

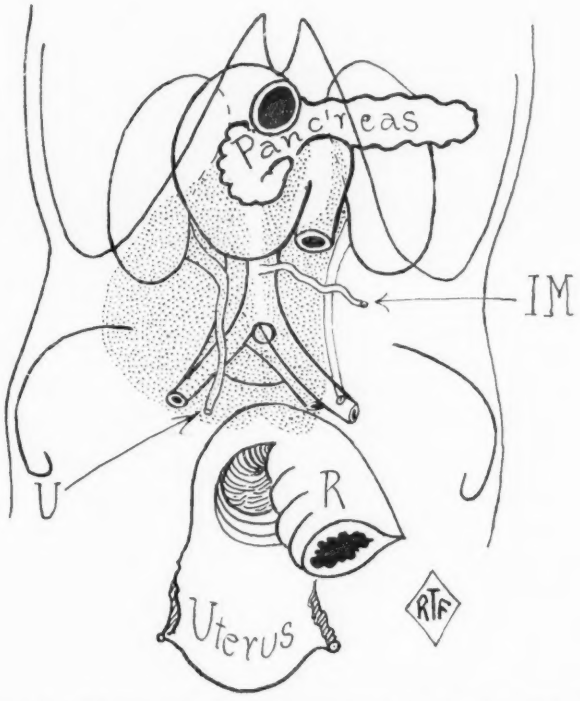

Fig. 6.—Case 2. Schema of retroperitoneal area, showing extent of growth.

(Figs. 4 and 5.) The lower pole of the growth was slowly developed, first from between the layers of the sigmoid mesocolon, then from behind the readily mobilized cecum, always keeping the intestine in view, profiting by dissectable layers. The growth was gradually pulled downward, vessels ligated as encountered, until its upper limit on the right side was finally reached (Fig. 6). The lower 10 cm. of the right ureter were embedded in a gutter of the tumor opening toward the right. The ureter was preserved. The upper limits of this portion of the growth covered the lower pole of the right kidney and ran behind the transverse portion of the duodenum. By now inserting the hand intraperitoneally above the obstructing transverse terminal iliac loop, it was discovered that another portion of the growth extended upward behind the stomach toward the diaphragm. This lobe of the tumor was developed by the same method and through the same posterior peritoneal opening. Great caution in following cleavage planes and visualization of anatomic landmarks was observed. The inferior mesenteric vessels lay between the right and left tumor masses, the left portion of which had likewise separated the layers of the

Fig. 7.—Case 2. Specimen. Two large flat masses joined by an isthmus situated over the division of the aorta. Smaller pedunculated growth near tail of pancreas and left crus of diaphragm. Weight, 4 pounds.

transverse mesocolon. A small outgrowth (Fig. 7) was removed in continuity with the left lobe and was situated on the left crus of the diaphragm.

The resulting huge retroperitoneal cavity (Fig. 6) was now carefully explored both by touch and as much as possible by vision. Small portions of the growth which had remained adherent to the transverse part of the duodenum were removed by the scalpel. The retroperitoneal cavity showed the lower pole of the right kidney, the right ureter throughout its length until it entered the pelvic cavity, the right psoas muscle, the vena cava, aorta, extraperitoneal portion of the duodenum as well as the tail of the pancreas. The inferior mesenteric vessels were completely isolated for several inches. The cavity appeared dry and therefore the posterior peritoneum was closed without drainage.

The patient made an uneventful and almost afebrile recovery until the tenth day when a phlebitis of the left leg developed. From January to March, 1937, Dr. William Harris gave the patient x-ray treatments to the pelvis and lumbar gutters. The dosage was as follows:

The factors used were kv. 200; filter 1 mm. copper 1 mm. aluminum; F.S.D. 50 cm.; size of fields, 15 by 20 cm.

Four fields were used: right and left lower quadrants and right and left buttocks. The right and left lumbar regions were also treated. Left lower quadrant received, 1,224 r. units*; right lower quadrant, 918 r. units; left buttock, 969 r. units; right buttock, 1,020 r. units; left lumbar, 1,020 r. units; and right lumbar, 2,100 r. units.

The patient has been followed and has completely recovered, with a gain of ten pounds. She still wears an elastic stocking for the chronic but subsiding edema of the left leg. She occasionally receives progynon dihydroestradiol tablets to control the flushes following x-ray steriliza-

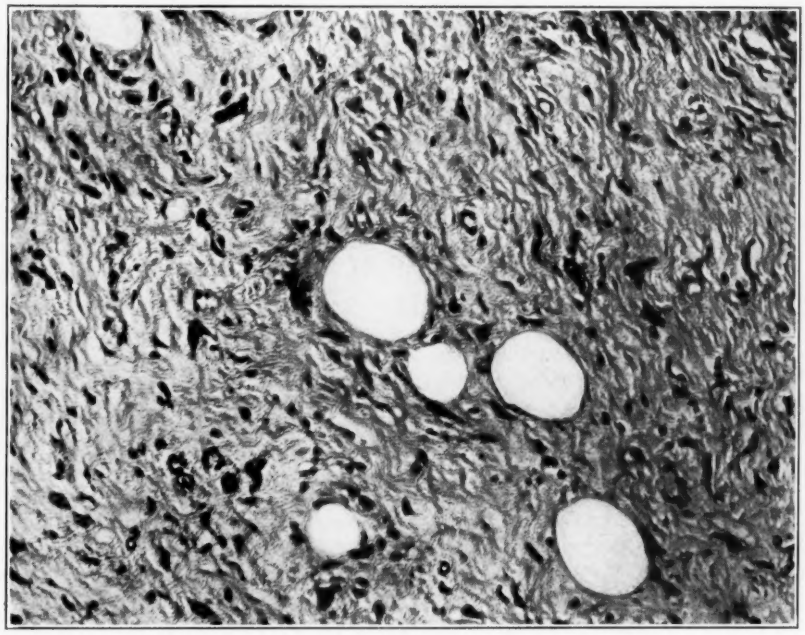

Fig. 8.—Case 2. Photomicrograph. Myxofibroliposarcoma.

tion. Abdominal examination is normal. Pelvic examination shows a small uterus, the fibroids having receded; normal Douglas and adnexae.

The pathologic report from Dr. Paul Klemperer, pathologist to the Mount Sinai Hospital, in abstract is as follows: The specimen consists of two large masses, one 25 by 12 by 5 cm., the other 15 by 14 by 9 cm. with a small pedunculated mass 5 by 4 cm. (Fig. 7). The weight was 4 pounds. The tumor was soft, almost fluctuant, and encapsulated. The cut surface was homogenous, pale brown to pink, and gelatinous.

Microscopic examination shows the tumor to be a fibrolipomyxosarcoma. The fat plays a very small part in the entire mass of the tumor, being largely microscopic. (Fig. 8.)

*r. units measured in air.

CASE 3.—There is a third case which I operated upon sometime between 1907 and 1912, the full details of which cannot be found. The patient was a young woman in her twenties, who complained of marked loss of weight and slow increase in size of the abdomen. The preoperative diagnosis was that of an unusually large ovarian cyst. Upon opening the abdomen, the entire abdominal contents appeared to be lying upon a water bed several inches in thickness, with prominence of the widely separated leaves of the mesentery of the small intestine. The hand, when introduced up to the diaphragm, noted continuation of the fluctuant mass to behind the liver. An avascular portion of the lower leaf of the separated mesentery was incised, a cleavage plane readily encountered. The cyst did not extend downward beyond the promontory and was entirely separate from the normal female genitals. A trocar was introduced into the cyst cavity and several gallons of a light brown fluid drained off. The cyst was then mobilized, purely by sense of touch. Very few vessels were encountered requiring ligation. After several feet of cyst wall had been drawn out through the abdominal wound, the lowermost posterior portion was found firmly adherent to the plainly visualized mesenteric vessels and could not be separated from their trunk. Therefore the redundant portions of the cyst were resected, the cyst edge sutured to the skin edge, and the residual cavity packed with a Mikulicz drain. The sinus closed in the course of some weeks.

This patient was followed for more than six years and remained in perfect health. She was then lost sight of. The cyst wall consisted of a fibrous layer lined with a single layer of low endothelium.

DISCUSSION

The literature of retroperitoneal growths not arising from any of the abdominal viscera has been collected by Steele, 1900,[90] Liebermann v. Wahlendorf, 1921,[62] Andrews, 1923,[3] Schmid, 1923,[87] as well as in several abstract reports from the Mayo Clinic, 1924-1932. (These, however, consist mainly of mesenteric tumors.) Judd and Larson[46] include tumors of the renal capsule, undescended testis, pancreas, and kidney (13 of 46 cases).

The repetitions and overlapping of these various articles are so confusing as to nullify any attempt at complete statistical presentation. A search of the literature between 1925 and 1936 shows 107 additional cases, excluding purely mesenteric and omental growths, as well as those specifically mentioned as arising from residual urogenital embryonic rests (Hansmann and Budd[36]).

The older literature appears to begin with Lobstein,[64] who in 1829 gave an accurate description of retroperitoneal growths including their gross characters and location. Virchow[97] in his *Geschwülste*, 1856, likewise mentions these growths. Gurlt[35] among 894 sarcomas (total cases, 16,637) found only 1 retroperitoneal growth, while Judd[45] in his recent statistics from the Mayo Clinic, found 25 mesenteric tumors in among 820,000 cases. Rasmussen[83] noted 9 retroperitoneal tumors in 42,000 patients. The older literature is referred to in detail by Steele.[90]

Origin.—The tumors in question have in common their derivation from retroperitoneal tissues, including fat, areolar connective tissue, fasciae, lymph glands, lymphatics, and sympathetic nervous structures.

It follows that the majority are mesodermal in character. Of the 107 cases from the literature, only the 20 neuromas and 10 teratomas may be considered of ectodermal derivation (28 per cent).

Site.—The tumors, *sensu strictu*, present behind the posterior layer of the peritoneum. During their development, they may raise any of the abdominal viscera away from the posterior abdominal wall and secondarily may extend into the mesentery of the large and small intestine as well as downward, over, or alongside the promontory of the sacrum, into the pelvic connective tissues and sigmoid mesocolon. They have grown into the inguinal canal (Lundblad[65]), Case 3, into the labium and buttock (Gough[33]), and through the sacrosciatic foramen (Lundblad, Case 16).

When these neoplasms attain large size, their point of origin no longer may be determinable, as they encroach upon and adhere to any of the intra-abdominal organs—kidney, adrenal, duodenum, small intestine, colon, stomach, liver, and even gall bladder (Gehrung, *see* Jackson[43]).

Size.—Tumors of the size of a fist (König[50]) up to gigantic growths weighing 63 German pounds (Waldeyer[98]) and 69 avoirdupois pounds (Hirsch and Wells[39]) are reported. In more recent times, such enormous proportions are less commonly observed although Gordon[32] in 1925 successfully removed a teratoma weighing 26 pounds; Harrington[37] in 1934 removed a fibromyxolipoma of 47 pounds and Williams[103] in 1935, a lipomyxosarcoma of 51 pounds.

Gross Characters.—The growths may be solid, cystic, or a combination of both, as the polycystic teratomas. Solid tumors, usually coarsely lobulated, are pseudofluctuant if lipomas, or myxosarcomas, firmer if fibrous tissues predominate; in a few instances, bony (Davidović[19]) or calcareous tissues (Harrington[37]) or both (Bode[10]) have been encountered. Even the malignant types, with the possible exception of round cell and fibrosarcomas, rarely show a markedly invasive tendency. The majority remain encapsulated. Small outgrowths, however, either connected by slender pedicles or entirely detached, are of frequent occurrence. These small growths are readily overlooked and may account for recurrence after apparently complete operative removal. This applies particularly to lipomas. Liebermann v. Wahlendorf,[62] after removing a lipoma weighing 7.000 gm., during the final revision of the wound bed, discovered and removed fifteen additional small growths.

The color of these growths varies between yellow (lipoma), grayish (myxosarcoma), white (fibroma), pinkish to red (sarcoma), variegated (teratoma), depending upon the predominant tissues.

The cystic tumors are thin walled and, according to the classification of Moynihan,[68A] consist of serous, chylous, hydatid, sanguineous, dermoid, and cystic sarcomas. The classification given by Cornioley[15] is almost identical. Lahey and Eckerson[55] add to these Wolffian (urogenital rests), mesocolic (residual peritoneal pockets), and traumatic or

blood cysts. The cysts consist of a fibrous wall with flat endothelial lining or devoid of a lining endothelium. The fluid content may be clear, sanguineous or fatty (dermoid).

Combination of solid and cystic portions result either from fluidification of parts of solid tumors such as lipomas, myxomas or sarcomas or are found in true embryomas which contain solid tissue, honeycombed by cysts.

Microscopic characteristics require no detailed description. The following summary of findings in cases submitted to microscopic investigation is taken from Liebermann v. Wahlendorf,[62] in 153 cases in which microscopic examination had been performed:

Pure lipoma		70 cases 45.7%
Mixed tumor		83 cases 54.0%
Fibrolipoma	31	
Myxoma	16	62 cases 40.5%
Fibromyxolipoma	15	
Sarcoma		21 cases 13.8%
Myxosarcoma	13	
Fibroliposarcoma	5	
Liposarcoma	3	

SUMMARY OF CASE REPORTS IN TABLE I

Of the 107 cases which I have collected from the literature between 1925 and 1936, there were:

Fibroma	8	Sarcoma	38
Lipoma	12	Neurogenic	20
Myxoma	11	Teratoma	10
		Cysts	8

107 cases collected
8 autopsy reports
98 operated
1 not operated
18 postoperative deaths
18.4% mortality:
29 cases were followed up:

Well 2½ mo.	1
Well 6 mo.	1
Well 1 yr.	4
Well 1¼ to 2 yr.	6
Well 2 to 3 yr.	6
Well 3 to 5 yr.	4
Well 5 to 10 yr.	2
Well 10 to 15 yr.	3
Well 15 to 16 yr.	2

Metastases are less common than local recurrences. In the older literature Waldeyer[98] described a lipomyxoma with small sarcomatous nodules in the liver and lungs. Of the 44 sarcomas collected by Steele,[90]

43 per cent showed metastases. Andrews[3] reports metastases in 33 per cent in the cases reported to 1923, occurring in liver, lungs, lymph glands, etc. Nikolski[72] (as noted in abstract) in 115 cases likewise noticed 33 per cent metastases. This is in marked contrast to the 107 cases which I report in which metastases were noted in only 4, 3.7 per cent, and of sarcomas, at the most, in 13.2 per cent.

Clinical Symptoms.—Small growths usually are discovered by accident either by the patient or by the examining physician. More usually, a slow, progressive enlargement of the abdomen is noted by the patient who eventually seeks medical advice. Vague digestive disturbances, such as anorexia, eructations, heartburn, colicky pains, and constipation, are complained of. Steele[90] found edema, especially of the lower extremities, neuralgic pains, and, in one case, femoral phlebitis. A progressive loss of weight and strength appears the universal rule. In rare instances acute abdominal symptoms have developed due to intraperitoneal rupture, peritonitis, or hemorrhage.

Hesse[38a] has described a difference in surface temperature of the two lower extremities as a sign of retroperitoneal growths due to pressure on the abdominal sympathetic nerves. At first the surfaces' temperature of the limb on the side of the lesion is diminished (stimulation of lumbar sympathetic). Later the temperature is increased as the pressure on the nerves decreases their conductivity. During the stage of decreased temperature, the pilomotor and sweat reflexes are increased (Zaiceva,[105] Vinogradov[96]).

Ileus (Burger and Osborne[12]), pyonephrosis due to pressure on the ureter, intraperitoneal hemorrhage (Dunet[21]), and rupture into the stomach (autopsy finding, Dahl[17]) are on record.

Termination.—If unoperated, and this is best noted in the older literature, a slowly progressive enlargement of the abdomen eventually leads to death from compression of the lungs by the elevation of the diaphragm, compressions of the intestine, kidneys, and ureters (case of Jackson,[43] 1889). Steele[90] reports two sarcomas of which one had perforated into the peritoneal cavity, one into the stomach. Dahl[17] likewise reports a case of gastric invasion.

Diagnosis.—Diagnosis will always prove difficult. Small growths are regularly considered of ovarian, uterine, hepatic, intestinal, or renal origin, depending upon their location, mobility, and the sex of the patient. Today, with the aid of gastrointestinal x-ray and pyelography, renal and intestinal growths may in the majority of instances be ruled out preoperatively. However, many of these growths, as can be seen from the summary of case reports, are perirenal in location and may be secondarily adherent to the kidney capsule or even parenchyma so that even these diagnostic aids may prove misleading.

TABLE

YEAR	TYPE	AUTHOR*	AGE	SEX	DURATION	SITE
1926	Fibroma	Dannheisser	37	M	–	Abd. retroperitoneal
1928	Fibromyoma	Kreiner	24	F	–	Abd. retroperitoneal
1929	Fibroma	Kanjan and Krivoborskaja	–	–	–	Abd. retroperitoneal and trans. meso.
1932	Fibroma	XIII Rankin and Major	25	F	1½ yr.	Retroperitoneal mesenteric
1933	Fibroma	Bader	40	F	Months	Retroperitoneal mesocolon
1934	Fibroma	Wolfer	31	M	5 yr.	Retroperitoneal
1935	Fibroma	V Rasmussen	45	F	–	Retroperitoneal
	Fibroma	VI Rasmussen	20	F	–	Retroperitoneal
1926	Lipoma	I Pritzi	62	F	5 mo.	Retrocolic left renal
1929	Lipoma	Hosemann	51	M	–	Retrocolic
1931	Lipoma	French	6	F	–	Perirenal
1931	Lipoma	II Burger and Osborne	61	M	–	Right iliac femoral
1932	Lipoma	III Lundblad	52	M	3 yr.	Iliac inguinal
	Lipofibroma	II Lundblad	63	F	–	–
1932	Lipoma	Bettman and Serby	40	M	7 mo.	Right retrocolic
1933	Lipoma	Pemberton and McCaughan	36	F	12 yr.	Perirenal
1933	Lipoma	Blaisdell	64	F	–	Retroperitoneal
1932	Lipofibroma	Quenu	42	F	–	Perirenal
1934	Lipofibroma	De Renzi	51	F	–	Subhepatic
1926	Lipomyxoma	Krogius	51	F	2 yr. +	Perirenal
1927	Myxoma	Gough	35	F	12 yr.	Abd. vulvar, gluteal
1930	Fibromyxoma	Lind	39	F	3 mo.	Retroperitoneal + pelvic
1932	Fibromyxoma	XIV Rankin and Major	50	M	10 yr.	Mesentery
1932	Lipomyxoma	Wechsler	65	M	3½ yr.	Retroperitoneal
1932	Lipofibromyxoma	I. Lundblad	46	F	?	Retroperitoneal
1932	Myxoleiomyoma	Nordland	26	M	–	Upper left retroperitoneal
1933	Fibromyxolipoma	Riche et al.	51	M	7 yr.	Left flank
1934	Fibromyxolipoma	Harrington	28	M	17 yr.	Retroperitoneal
1934	Fibromyxoma	I Phillips	63	F	4 yr.	Gastrohepatic
1934	Fibromyxolipoma	Pemberton and Whitlock	47	F	1 yr.	–
1929	Sarcoma	Guleke	–	–	–	Retroperitoneal
1932	Sarcoma	Duroselle	64	F	–	Perirenal
1932	Sarcoma	Newton	17	F	Months	Retrocecal
1932	Sarcoma	Didiée	–	–	–	Retroduodenal
1934	Sarcoma	Walters and Priestley	43	M	–	Mesosigmoid
1926	Fibrosarcoma	II Pritzi	41	F	4 mo.	Retrocecal and sigmoid
1934	Spindle cell sarcoma	II Lepoutre	64	F	–	Perirenal
1932	Spindle cell	VI Lundblad	48	F	1 yr.	Presacral
	Telangiectatic sarcoma	IV Lundblad	55	F	–	Retrocecal and perirenal
	Telangiectatic sarcoma	V Lundblad	30	M	4 mo.	Retrocolic
	Lymphosarcoma	VII Lundblad	65	F	Years	Retroperitoneal

*Where more than one case was reported by the same author, the Roman numerals refer to the number of the case in the article quoted.

†*Lap.*, laparotomy; *op.*, undescribed operation.

I

OPER.	RESULT	WEIGHT	
Lap.†	Recovered	4,750 gm.	Bladder twice injured; no follow-up
Lap.	Recovered	10 by 16 by 12 cm.	
Lap.	–	–	In 3 divisions
Lap.	Recovered	11 by 8 by 7 cm.	Intestinal resection
Lap.	Recovered	4.2 kg.	Resected tranverse colon; well 2 yr. postoperatively
Lap.	Recovered	16½ lb.	Later pleuroabdominal fistula; 2 mon. convalescence
Lap.	Recovered	–	Well 14 yr. postoperatively
Lap.	Recovered	–	Well 15 yr. postoperatively
Lap.	Recovered	Large	Nephrectomy
2 op.†	Recovered	–	Died 7 yr. after second operation from recurrence
Op.	Recovered	635 gm.	
Lap.	Recovered	8 by 5 by 5½ cm.	Extension into femoral canal
Lap.	Recovered	–	Extension into inguinal canal
Op.	Recovered	3½ kg.	Well 3 yr. postoperatively
Op.	Recovered	22½ lb.	Ureter in tumor; nephrectomy
Lap.	Recovered	850 gm.	Adherent to lower pole right kidney
Op.	Recovered	250 gm.	Like actively proliferative bone marrow
3 op.	Recovered	–	Operations for 2 recurrences in 5 yr.
Lap.	Recovered	–	Given x-ray; died
Lumbar	Recovered	6,150 gm.	Previous exploratory lap. 2 yr. ante
Labial and buttock	Recovered	10 lb.	Intra-abdominal untouched; excised labial and buttock
Lap.	Recovered	2,900 gm.	
Lap.	Recovered	25 lb.	
Exploratory	Died 6 wk.	25 lb.	Adherent stomach, colon, tumor ruptured (aspiration!)
5 op.	Recovered	9 kg.; 7⅘ kg.	Alive 6 yr. after last operation
Lumbar	Recovered	16 by 8 cm.	Well 2¼ yr. postoperatively
3 op.	–	1640 gm. 1,300 gm.	3 operations; infiltrating muscle at last operation
Lap.	Recovered	47 lb.	With calcification and necrosis
Lap.	Died 1 day postoperatively	4,196 gm.	Adherent to postgastric wall
Op.	Recovered	10 kg.	
Lap.	Recovered	–	Died ¾ yr. postoperatively
Op.	Recovered	Child's head	Well 7½ yr. postoperatively
Exploratory	Recovered	–	Ra. needles, well 1 yr. later
Autopsy	–	–	From retroduodenal nodes
Lap.	Recovered	–	Deep x-ray postoperatively; well 1 yr. later
Lap.	Recovered	–	Sigmoid injured, "Vorlagerung"
Op.	Recovered	–	Died 9 mo. postoperatively with metastasis
Lap.	Recovered	Large	Alive 11 yr. postoperatively
Lap.	Recovered	–	1 lit. bl. in abd., duod. inj. died 6 mo. postoperatively
Lap.	Died 10 days postoperatively	–	–
Lap.	Recovered	–	Died 2 yr. postoperatively

TABLE I

YEAR	TYPE	AUTHOR*	AGE	SEX	DURATION	SITE
	Polymorph. & lymph	VIII Lundblad	34	F	1 mo.	Retrocolic
1933	Spindle cell sarcoma	Eliason and Ferguson	38	F	8 mo.	Transverse mesocolic
1933	Fibrosarcoma	Judd and Larson	–	M	2 yr.	Perirenal
1933	Fibrosarcoma	Arenas	32	F	7 mo.	Perirenal
1933	Fibrosarcoma	MacLeod	55	M	6 mo.	Perirenal
1934	Spindle cell	Suzuki	12	M	6 mo.	Retroperitoneal
1934	Spindle cell	Craciun et al.	55	M	–	Retroperitoneal
1934	Fibrosarcoma	I Dahl	74	F	–	Retroperitoneal
1934	Lymphosarcoma	Irwin	47	F	1 mo. ?	
	Round cell sarcoma	I Burger and Osborne	49	M	2 mo.	Upper right retroduodenal
1932	Lymphosarcoma	Castellano et al.	39	M	–	Retroduodenal
1932	Angiosarcoma	Beitzke	38	F	–	Retroperitoneal
1929	Polymorphous	Nikolski	26	F	1 mo.	Retroperitoneal
		Nikolski	48	F	5 mo.	Retroperitoneal
		Nikolski	50	F	5 mo.	Retroperitoneal
	Leiomyosarcoma	IV Phillips	42	M	1 yr.	Perirenal
1931	Myxosarcoma	III Burger and Osborne	47	F	5 mo.	Retrocecal
1925	Fibromyxosarcoma	Tammann	60	M	5 yr.	Retroperitoneal
1925	Fibromyxosarcoma	Leichner	48	M	1 mo.	Retroduodenal
1928	Fibromyxosarcoma	I Kreiner	32	F	1 yr.	Retrocolic
	Fibromyxosarcoma	III Kreiner	70	F	–	Gastrocolic and retroduodenal
1928	Myochondro-osteofibrosarcoma	II Davidović	–	–	–	
	Fibromyosarcoma	I Davidović	–	–	–	
1931	Myxosarcoma	Kitamura	69	M	–	Retroperitoneal
1931	Fibromyosarcoma	Bange	56	M	2 yr.	Perirenal
1934	Liposarcoma	I Lepoutre	32	F	–	Perirenal
1935	Lipomyxosarcoma	Williams	65	F	4 yr.	Perirenal
1925	Neuroma	Krumbein	49	M	–	Perirectal
1927	Ganglion-neurofibroma	Neumann	14	F	–	Retroperitoneal pelvic
1929	Neurinoma	König	28	M	–	Cava and sacroiliac joint
1929	Ganglion neuroma	Guleke	–	–	–	–
1931	Gliosarcoma	Bode	8 M	fetus	–	Retroperitoneal
1931	Ganglioneuroma	McFarland	12	F	–	Lap.
1932	Ganglioneuroma	Hortolomec et al.	50	F	–	Retrocolic
1932	Neurogenic sarcoma	Adair	13	M	–	Pelvic
1932	Fibroneurinoma	IX Lundblad	41	F	1 yr.	Retroperitoneal
	Fibroneurinoma	X Lundblad	52	F	–	Retroperitoneal
	Neuroma ganglinare	XI Lundblad	29	M	7 mo.	Pelvic
1933	Sympathicoblastoma	Fels	32	F	–	–
1933	Schwannoma	Frank	30	F	7 yr.	Retropelvic

—CONT'D

OPER.	RESULT	WEIGHT	
Lap.	Died 1 day postoperatively	Large	–
Lap.	Recovered	8 cm. diameter	Well 4 yr. postoperatively
Op.	?	1 kg.	1930, fibroma removed; nephrectomy
Lap.	Died 1 day postoperatively	–	Adherent to intestine
Op.	Recovered	Huge	Nephrectomy
Op.	Died	930 gm.	No metastases
Autopsy	–	–	From retroperitoneal lymph glands
Autopsy	–	–	Had ulcerated into stomach
Autopsy	–	–	Advanced retroperitoneal sarcomas
Op.	Died	–	Died of shock
Exploratory	–	Size fist	Biopsy
Autopsy	–	–	Metastasis lungs and lymph nodes
Lap.	Recovered	–	Vena cava torn and sutured; in 6 months, metastasis
Lap.	–	–	Nephrectomy
Not op.	–	–	Inoperable
Exploratory	Died 3 wk.	22 lb.	
Lumbar second op.	Died 5 wk. postoperatively	–	Obstruction 5 weeks postoperatively from retroperitoneal invagination and intussusception by recurrence
Lap.	Recovered	3,300 gm.	Well 2½ mon. postoperatively
Lap.	Recovered	15 cm. diameter	
Op.	Recovered	Size fist	Given x-ray; well 1½ yr. postoperatively
Lap.	Recovered	Man's head	Adherent to liver, cava, kidney vessels; well 1½ yr. later
Op.	Died weeks postoperatively	–	
Op.	Died	–	
Lumbar	Recovered	4,300 gm.	
Lumbar	Recovered	345 gm.	Nephrectomy (pyonephrosis); no follow-up
Second op. lumbar	Died 3 mo. 2nd p.o.	–	First operation removed large and 4 small tumors Second operation 9 mo. later with nephrectomy
4 op.	Recovered	51 lb.	One exploratory, biopsy, lipoma; 2.2 yr. later, 51 lb. with nephrectomy sarcoma; 3.5 yr. later, peritoneal infiltration; 4.3 yr. later, exploratory
Lap.	Died	–	Rectum torn, peritonitis
Lap.	–	–	Solid, only partial removal
Lap.	Recovered	9 by 11 cm.	Right ureter anterior to mass
Lap.	Recovered	Man's head	Well 2½ yr. postoperatively
Autopsy	–	–	Contained also bone and cartilage
Op.	Died 3 days postoperatively	Large	–
Lumbar	Recovered	–	Well 1 yr. postoperatively
Exploratory	Recovered	–	Biopsy, deep x-ray; well 2½ yr. postoperatively
Lap.	Recovered	–	Well 2 yr. postoperatively
Lap.	Recovered	–	Well 1 yr. postoperatively
Lap.	Recovered	20 cm. diameter	Injured urethra and prostate; well 4 yr. postoperatively
Lap.	Recovered	–	No follow-up
Lap.	Recovered	Cystic	Well 5 yr. postoperatively

TABLE I

YEAR	TYPE	AUTHOR*	AGE	SEX	DURATION	SITE
1933	Ganglioneuroma	Schleifstein	18	F	–	Retroperitoneal
1934	Sympathicoblastoma	Garofalo	3	–	–	Perirenal
1934	Sympathicoblastoma	Mosto and Echegaray	6	M	3 yr.	Retroperitoneal
1935	Neurogenic sarcoma	Smith and Armstrong	31	M	–	Retroperitoneal
1936	Sympathicoblastoma	Wendel	6	F	–	Lumbar
1936	Neurinoma	I Vinogradov	38	F	–	Retroduodenal
	Neurinoma	I Vinogradov	25	F	4 yr.	Perirenal
1925	Teratoma	Gordon	50	F	3 mo.	Retroperitoneal
1931	Teratoma	Usandizaga and Mayor	28	F	–	–
1932	Teratoma	XIV Lundblad	4	F	–	–
	Teratoma	XV Lundblad	4	F	–	Lumbar
	Teratoma	XVI Lundblad	25	F	–	Pelviabdominal
1932	Teratoma	Froboese	¼	F	1 yr.	Retroperitoneal
1934	Teratoma	Watanabe	2	M	–	Retroperitoneal
1934	Chorionepithelioma	Fenster	27	M	1 yr.	Lumbar
1935	Teratoma	Landivar and Iparraguirre	45	M	3 mo.	Retrogastric
1935	Teratoma	Nicholson	7 M	F	5 mo.	Retroperitoneal
1930	Lymph cyst	Durst	–	–	–	Retroperitoneal
1931	Lymphangioma	Burhaneddin	40	M	3 yr.	Retrocolic
1931	Sanguineous cyst	Shands	49	F	–	Retrocecal
1934	Lymphangioma	Kretschmer and Hibbs	59	F	–	Perirenal
1935	Hemangio-endothelioma	Steinert	33	F	–	Hepatic duodenal
1935	Sanguineous cyst	IV Rasmussen	14	F	–	Retroperitoneal
1925	Lymph cyst	Cornioley	35	F	–	Retrocecal
1932	Serous cyst	XIII Lundblad	M	39	–	Retroperitoneal

NOTE.—Neither mesenteric tumors nor growths of the great omentum, unless secondarily extending from a retroperitoneal site, have been included in the table.

In a recent case of a tumor presenting below the spleen, the pyelographic evidence could be interpreted as favoring renal origin. However, because of its intra-abdominal rather than lumbar location, I entered the abdomen by a transperitoneal paramedian incision. The mass proved to be a large solitary cyst of the lower pole of the left kidney developed mesial to the descending colon. Only when the intimate adherence of the cyst to the kidney parenchyma had been demonstrated, necessitating resection of part of the lower pole, was the point of origin determined.

A description of the differential diagnosis by means of x-ray will be found in Stepp and Böger.[92]

Some of the larger growths show the transverse colon coursing over the anterior surface of the tumor in a well-formed gutter. More commonly the ascending or descending colon is crowded toward the median line. Only in centrally located growths does the large bowel surround the circumference of the growth, the small intestine being compressed upward or downward. In the retroperitoneal cyst which I previously described (Case 3), the entire abdominal content appeared lifted off

—CONT'D

OPER.	RESULT	WEIGHT	
Exploratory	Recovered	Large	Incomplete operation; alive 1½ yr. postoperatively
Lumbar	Recovered	–	Recurrence with metastasis, 5 yr. postoperatively
Exploratory	Died 6 hr.	2 kg.	Adherent to big vessels
Op.	Recovered	–	–
Exploratory	Died 4 mo. postoperatively	Large	Exploration for intestinal obstruction
Lap.	Recovered	Small	Well 2 yr. later
Op.	Recovered	–	Ecto- and mesoderm
Lap.	Recovered	26 lb.	2 germ layers-hair-bone-cysts; nephrectomy
Op.	Recovered	–	Mesodermal
Op.	Died	Large	Ecto- and mesoderm
Lumbar	Recovered	–	Died 8 mon. postoperatively, mainly entoderm
Lap. and parasacral	Died 11 days postoperatively	Large	Cerebral embolism; Polycystic ecto-, meso-, and entoderm
Autopsy	Died at 1¼ yr.	–	Between kidney and liver; mainly entoderm
Autopsy	Died	660 gm.	Tridermal with carcinomatous metastases
Exploratory	Died	Large	Inoperable; testis in serial section normal
Lap.	Recovered	1,750 gm.	Well 3 yr. postoperatively; 3 germ layers
Op.	Recovered	2½ lb.	Ecto- and mesoderm; well 4¼ yr. postoperatively
Op.	Recovered	–	Well 1¼ yr. postoperatively
Op.	Recovered	6.4 kg.	No follow-up
Op.	Recovered	–	–
Lumbar	Recovered	8.5 by 11 by 9 cm.	Single flat layer endothelial cells
Lap.	Recovered	7 cm. D.	Symptoms duodenal ulcer; well 6 mon. postoperatively
Lap.	Recovered	–	Well 16 yr. postoperatively; cyst without epithelial lining
Lap.	Recovered	22 by 17 cm.	Epithelial lined
Lap.	Recovered	Very large	Inferior mesenteric artery in wall; died 11 yr. later from tuberculosis

from the posterior abdominal wall. Pseudofluctuation, characteristic of lipomas and pseudomyxomas in females, regularly leads to the conclusion that an ovarian cyst is present. In my Case 2 pregnancy appeared to have been suspected before I saw the patient. Tuberculous peritonitis and hypernephroma are among the preoperative diagnoses.

In Froboese's case,[30] later demonstrated as a teratoma, Zondek[106] found a I and III gonadotropic reaction in the patient's urine. Similar reactions were obtained by Fenster[26] in a primary retroperitoneal chorionepithelioma (serial sections of both testes normal).

Treatment.—Operation offers the surest prospect of permanent relief and cure. Andrews,[3] who reported 28 cases of retroperitoneal sarcoma from the Mayo Clinic in 1923, however, found that 20 of the 27 patients were already in an inoperable condition when first seen (sarcomas). In the older statistics the operative mortality was discouragingly high. Hosemann[41] found 25 to 38 per cent. Schmid,[87] of 133 cases operated upon between 1903 and 1922, noted a reduction of mortality to 7½

per cent. In the 107 cases collected by me, 99 are available in this connection as 8 were autopsy reports. Of the 98 patients operated upon, 18 died from the operation, an operative mortality of 18.4 per cent.

A marked difference in operative mortality is noted, depending upon the nature of the growth.

	OPERATIVE MORTALITY
Fibroma, lipoma, and cysts (28 cases)	0%
Myxoma (11 cases)	18.8%
Neurogenic (19 cases)	22%
Sarcoma (38 cases)	28.13%
Teratoma (8 cases)	36.7%

Both the operability and risk incurred depend partly upon the location, extent, adherence to, and involvement of vital or inaccessible structures; but the histology plays a more decisive role. In the older literature there is a report of Braun,[11] who resected 2 cm. of the aorta below the renal arteries, in the removal of a retroperitoneal growth, with survival of the patient. Nikolski[72] reported a lateral tear of the vena cava, suture, recovery. In many instances the ureters or renal vessels were injured, necessitating nephrectomy. Injuries to the duodenum (Lundblad[65] Case IV), bladder (Dannheisser[18]), transverse colon (Bader[5]), and rectum (Krumbein[54]) occurred during removal. Resection of the small intestine has been performed repeatedly. In a case of a mesenteric sarcoma, not reported in this series, Judd, Counsellor, and Hoerner[44] resected all but 30 cm. of the terminal ileum, the patient recovering. In retroperitoneal growths intestinal resection is most often necessitated by injury to, followed by ligation of, the inferior mesenteric, middle colic, or sigmoid vessels with resulting impairment of the vitality of the intestine.

The method of approach utilized has depended largely upon the preoperative diagnosis or was based on the location of the mass. The majority of incisions have been paramedian, transperitoneal (84.6 per cent of 79 cases). For distinctly laterally located tumors a lumbar incision has been practiced, such as is used for kidney operations. This, when necessary, has been extended anteriorly. Frequently the lateral retroperitoneal approach has been converted into a transperitoneal one. Lundblad (Case XVI) performed a transperitoneal operation and completed the removal pararectally from below.

Härtel[38] has given a detailed anatomic description, well illustrated, of the anatomy of the posterior and lateral abdominal spaces as well as that of the attachment of the mesentery. In transperitoneal approach to the growth the apex of the tumor usually will present. As a rule the posterior peritoneum can be split over the most prominent part unless this endangers the blood supply of the small intestine or colon.

If the site is more lateral, the posterior peritoneal incision should be placed external to the ascending or descending colon, which may then be mobilized toward the midline. In a growth of the upper abdomen Kreiner[51] found it necessary to incise and ligate the gastrocolic ligament. Through this approach he successfully detached a fibromyxosarcoma from the duodenum, posterior surface of the liver and diaphragm.

Cleavage planes should always be sought for. Deliberation, gentleness in handling tissues, careful search for ureters, inferior and superior mesenteric vessels, the great vessels of the abdomen, duodenum, pancreas, particularly the renal veins, will forestall injury to these important structures and thereby reduce the operative risk. It may be preferable, as I found in the case of schwannoma,[27] as well as Cases 2 and 3 here reported, temporarily to leave particles of tumor behind, with careful notation of their location, until the main mass has been delivered. The operative site is then so much more accessible that minute dissection of these residua is greatly facilitated.

In every instance, after the tumor has been removed, careful search for detached or completely separated growths must be instituted. As an example, the 15 additional lipomas found by Liebermann v. Wahlendorf may be cited. In my Case 2 the two large tumor masses were joined together below by an isthmus, in addition to which there was a small pedunculated growth attached to the left mass (Fig. 7). Kanjan and Krivoborskaja[48] found three unconnected tumors, soft fibromas of equal size, widely separated—left hypogastrium, presacral, and under the transverse mesocolon.

Reoperations for recurrences have been performed. Hosemann[41] reported that, of seven cases operated upon twice, all died of recurrences. In my series, in addition to Hosemann's case, Quenu,[81] Lundblad[65] (Case I), Burger and Osborne,[12] Lepoutre,[60] and Williams[103] operated two or more times. After a number of incomplete operations, patients have survived over varying periods of time. The treatment of these growths in some ways resembles that of pseudomyxoma peritonei, in which repeated operation may prolong life for many years. Lundblad, Case I,[65] performed five operations; the patient was alive six years after the last operation.

Radiotherapy, according to Lind[63] and also Hosemann,[41] is useless for lipomas. It has proved, however, of service when inoperable conditions are encountered. Newton's[70] patient treated with radium needles inserted in the tumor (sarcoma) was well one year later. De Renzi's[84] case, a lipofibroma, was given x-ray treatments but died. Walters and Priestley's[99] case of sarcoma after operation and deep x-ray was well one year later. Kreiner's[51] Case 1, a fibromyxosarcoma, was well one and one-half years. Adair's[1] case of neurogenic sarcoma, merely explored, after x-ray was well two and one-half years. My own Case 1,

biopsy (mesenchymal), is well eight and one-half years after use of radium pack and deep x-ray; Case 2 received deep x-ray postoperatively and is well one and one-fourth years after operation. It appears well justified to give deep x-ray therapy postoperatively in this type of case.

Granulomas.—In Schiller-Christian disease large retroperitoneal granulomas may arise. Oberling[75] describes three cases successfully operated upon. In Case 2 the mass weighed 3 kg. Juhl[47] encountered an apple-sized nonspecific granuloma between aorta and ascending colon in a 26-year-old female. Blaisdell,[9] in the fatty tumor he removed (see Table I) noted hematopoiesis as in actively proliferating bone marrow. A similar condition may account for the 10 per cent eosinophilia described by Leichner.[59]

SUMMARY

Primary retroperitoneal tumors, although unusual, occur with sufficient frequency to make it advisable for the surgeon to familiarize himself with the subject.

1. They develop retroperitoneally behind the intra-abdominal viscera. Mesenteric and omental growths are not included in this presentation.

2. The majority of the growths are of mesodermal origin (72 per cent). The remainder are of ectodermal (neurogenic, 18.7 per cent) or from totipotential germ cell derivation (teratomas, 9.3 per cent).

3. Tumors may attain huge size; those weighing up to 69 pounds have been reported. They may be solid, cystic, or a combination of both. With the exception of the round cell sarcomas, the majority are well encapsulated. Multiple, often unconnected masses are frequent and particularly in lipomas and myxomas account for "recurrences" if overlooked.

4. The histology shows benign lipomas, fibromas, and cysts; of doubtful clinical malignancy, myxomas; definitely malignant, sarcomas, neuromas, and teratomas.

5. In the present series recurrences were noted in 14 (13 per cent); metastases, in 4 (3.7 per cent). In the older series 33 per cent metastases were found.

6. The clinical symptoms are not characteristic. Loss of weight and strength, an abdominal mass (central or lateral), and vague digestive disturbances are the rule.

7. Without operative intervention a fatal outcome from the increase in size and the pressure exerted may be anticipated even from benign growths.

8. Gastrointestinal x-ray and pyelography may aid in the diagnosis by excluding intrinsic intestinal and renal growths.

9. Depending on the sex, site, and associated symptoms, the preoperative diagnosis most often is that of fibroids, ovarian cysts, hypernephroma, tuberculous peritonitis.

10. Imperative indications for operation may arise if ileus, hydronephrosis or pyonephrosis, or intraperitoneal hemorrhage supervenes.

11. Operation offers the greatest prospect of cure. In the series of 107 cases, deducting the 8 autopsy reports, only 10 were found inoperable (10.1 per cent). Of these 10, 3 were alive 1 to 2½ years later after radium and x-ray treatment.

12. Transperitoneal approach was utilized in 66, lumbar or combined in 13, not stated in 19 cases.

13. The operative risk incurred depends mainly upon the histologic type of tumor. Mortality was zero in fibroma, lipoma, and cyst; it increased progressively in myxoma (18.18 per cent), neurogenic tumors (22 per cent), sarcoma (28.13 per cent), to teratoma (36.7 per cent).

14. Radiotherapy (radium pack, high voltage x-ray) is indicated in all inoperable or incompletely operated cases. It is recommended postoperatively except if fibroma or lipoma is encountered.

15. Three new cases are reported—embryonal mesodermal tumor (exploratory), radium pack and deep x-ray, well 8½ years; myxoliposarcoma, operated, postoperative x-ray, well 1¼ years; retroperitoneal cyst, marsupialized, well 6 years.

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HYPERTROPHY OF THE LIGAMENTUM FLAVUM

With a Report of Two Atypical Cases

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HYPERTROPHY of the ligamentum flavum with compression of the contents of the spinal canal has been rarely noted until recently. Spurling, Mayfield, Rogers[1] and Naffziger, Inman, and Saunders[2] have adequately discussed the etiology, the normal and pathologic anatomy, the usual symptomatology, and the treatment of the condition. The lesion is a simple hypertrophy of the ligament with no neoplastic or inflammatory element. In all probability, repeated stresses and strains, incident to heavy physical labor, constitute a factor in its production. The symptomatology is related both to local change in the spine and to compression of the dural contents. In all previously reported cases the involved ligament has been in the lumbar or lumbosacral area and a remarkably constant syndrome has been present, consisting of "pain low in the back with neurological signs of compression of the cauda equina," as pointed out by Spurling, Mayfield, and Rogers.[1]

Two cases of the disease under consideration are made the subject of this report because of certain atypical pathologic and clinical features not hitherto recorded in this condition.* In each, the presence of an hypertrophied ligamentum flavum was demonstrated both grossly and microscopically.

CASE REPORTS

Case 1.—Colored adult, male, admitted with pain in the back and legs and numbness of legs. No history of trauma. Complete block by Queckenstedt test. Cisternal lipiodol blocked at the fifth thoracic vertebral level. Laminectomy disclosed thickened ligamentum flavum. Discharged much improved. Second admission (nine months after discharge) with recurrence of symptoms. Queckenstedt test again demonstrated complete block. Reoperation advised and refused. Third admission (one month later), reoperation disclosed recurrence of the condition in the next highest ligament. Again discharged slightly improved. Sudden death from unknown cause at home two months after last operation. No autopsy.

George W. (University of Virginia Hospital, No. 103330), colored, aged 47 years, married, a laborer, was first admitted May 8, 1933, and discharged improved on June 29, 1933. He had been a steady drinker and smoker for many years. He was well until five weeks before admission when diffuse pain occurred, beginning in the back and radiating to the epigastrium and thorax. Three weeks before admission, weakness in the legs was noticed, increasing in severity until a cane was

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*For the purposes of record and contrast, two typical cases from this Clinic are summarized in a supplementary note.

necessary to aid walking. Numbness of the legs began at the same time as the weakness. There was no sphincter disturbance.

On examination the deep tendon reflexes of the lower extremities were found to be exaggerated. There was an indefinite sensory level at the sixth thoracic dermatome. No sensory dissociation was present. There was loss of vibratory sensation in each leg together with moderate impairment of the sense of position. There was atrophy of each leg. Lumbar puncture showed an initial pressure of 60 mm. of water with a complete subarachnoid block.

The blood Wassermann was two plus. X-ray examination of the spine disclosed marked osteoarthritis between the anterior margins of the bodies of the eighth to the tenth thoracic vertebrae. Five days after admission, a combined lumbar-cisternal puncture was carried out which verified the previously demonstrated block and showed, in addition, increased globulin in the lumbar fluid. Iodized oil (0.75 c.c.) placed in the cisterna magna revealed a block at the fifth thoracic vertebral level after the patient had sat erect for two hours (Fig. 1).

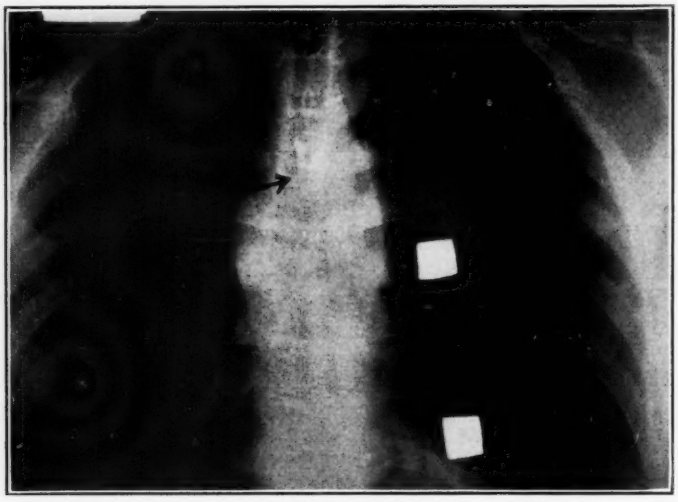

Fig. 1.—Case 1. Lipiodol (0.75 c.c.) introduced into cisterna magna revealing a complete subarachnoid block at the fifth thoracic vertebral level.

Ten days after admission, laminectomy was carried out (E.P.L.) under gas-oxygen anesthesia. An excerpt from the operative note reads: "The spines of the third to the sixth thoracic vertebrae were removed. The soft tissues appeared edematous and injected. The laminae were rongeured away from below upward. At the upper level of the fifth thoracic vertebra, a yellow mass was found lying over the dorsum of the dura. Additional bone was removed to a distance of 2 cm. above the lesion. The mass was 15 mm. in thickness. It was cartilaginous in consistency and attached to the periosteum. The tissue was bright yellow in color and was easily brushed away from the dura. The mass was dislodged from the lateral recesses and entirely removed, three-fourths of the circumference of the dura being involved. A curved impression in the dura resulting from the overlying mass was quite evident. The dura was not opened because of the possibility of the lesion being of an inflammatory nature. The dura was pulsating at the close of the operation below as well as above the site of the lesion."

The pathologic examination disclosed a mass of heavy fibrous tissue (Fig. 2). This was interpreted as normal ligamentum flavum although there was lymphocytic

infiltration about the vessels in the adventitiously included epidural fat, suggestive of syphilis. No tubercle bacilli were disclosed by special stains.

Three days after operation, there was noted considerable improvement in sensation, including sense of position and vibration in the lower extremities. Progressive improvement continued and he was discharged on June 29, 1933, forty-two days after operation. A follow-up letter six months after discharge stated that the patient was back at work as a laborer.

The patient was admitted for the second time on March 5, 1934, about eight months after discharge, and left the hospital on March 19, 1934, having refused operation. He stated that he had been making progressive improvement and was back at work at hard manual labor until one month previously when, after four hours of snowshoveling, numbness and weakness of the legs again suddenly supervened.

On examination, the patient was scarcely able to walk, even with the aid of crutches. There were no definite sensory changes found, although painful sensations and temperature appreciation in the legs were poorly detected by the patient. Position sense and vibratory sense in the lower extremities were practically absent.

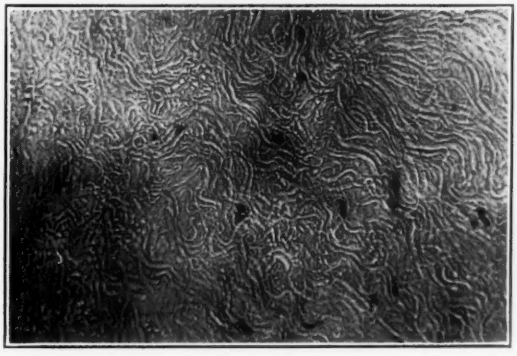

Fig. 2.—Case 1. Photomicrograph of elastic tissue removed at first operation of undoubted normal ligamentous structure (×230).

There was a suggestive ankle clonus on the right side but no Babinski sign could be elicited. The Romberg test showed considerable ataxia.

Lumbar puncture disclosed an initial pressure of 100 mm. of water. After the removal of 7 c.c. of fluid, the pressure was only 25 mm. of water. Complete subarachnoid block was again present. Examination of the fluid showed the presence of three-plus globulin, six lymphocytes, and a negative Wassermann reaction.

The patient was readmitted for the third time on April 6, 1934, eighteen days after the second discharge. At operation (E.P.L.) an hypertrophied ligamentum flavum was found at the fourth thoracic vertebral level and below this area a marked amount of extradural inflammatory tissue was disclosed. As much of this tissue as possible was removed. The dura was opened and marked arachnoiditis and injection of the cord were seen, to be ascribed, probably, to the lipiodol injected prior to the first operation. No resistance was met to the passage of a blunt instrument up and down the subarachnoid space.

Pathologic examination of the tissue removed at the second operation disclosed fragments of necrotic bone embedded in what appeared to be typical tuberculous granulation tissue. It was composed of small, often confluent, nodules of epithelial cells, among which were numerous giant cells; in addition, numerous small areas of caseation were seen. The whole tissue was infiltrated by lymphocytes. (Fig. 3.) A

few characteristic acid-fast bacilli were demonstrated in the caseous areas. Attached to one of the masses of granulation tissue was a thick layer of dense, collagenous fibrous tissue. There were also several small masses of elastic tissue which showed no pathologic changes. *Diagnosis:* Ligamentum flavum; tuberculous granulation tissue; fragments of necrotic bone.

The patient was discharged thirty-four days after operation, being able to move his legs fairly well and walking with support. There was improvement in pain appreciation and in heat and cold discrimination in the legs. Vibratory sense of the lower extremities was still diminished. These findings were interpreted as showing improvement over the preoperative status at the time of the third admission. Antisyphilitic therapy was carried out, postoperatively, before the patient was discharged.

He became suddenly ill and died in a few days, about a month after final discharge from the hospital and over two months following the second operation. Details of his final illness are not known and no post-mortem examination was possible.

Fig. 3.—Case 1. Photomicrograph of tissue removed at second operation. Dense fibrous tissue of the ligamentous type is seen. The central lesion (arrow) is suggestive of a chronic granulomatous infection, superimposed on hypertrophy of the ligament (×120). (Tubercle bacilli were found by carbol-fuchsin stain.)

Case 2.—White adult, male, admitted complaining of weakness of the legs of three months' duration without pain or sensory disturbance. X-ray examination after iodized oil injection showed a filling defect at L_3 vertebral level. Markedly increased globulin content of cerebrospinal fluid. Laminectomy disclosed hypertrophy of the ligamentum flavum. Dura opened. No evidence of tumor. On discharge thirteen days postoperatively, no essential change in neurological findings.

Carl D. (University of Virginia Hospital, No. 131682), white, aged 23 years, married, a rayon mill worker, was admitted May 17, 1937, and discharged June 13, 1937. His chief complaint was weakness of the legs of three months' duration. Eleven months before admission he had noticed weakness of his knees after jumping across a creek. For the last three months, there had been a slowly progressive weakness of the lower extremities. A lumbar puncture performed a few days before admission revealed 130 mg. of protein per 100 c.c. of spinal fluid.

On examination, he was found to walk with a toedrop gait. There was marked bilateral weakness of the peronei and anterior tibial muscles. The calves of the legs were large and the muscles were soft and boggy. There was no sensory disturbance in any modality, and no pain in the back or in the legs was present. The knee jerks and the ankle jerks were absent. No pathologic reflexes could be elicited. The blood Wassermann and Kahn both were negative. X-ray films of the lumbodorsal spine were normal.

Three days after admission, lumbar puncture showed a protein content of 430 mg. per cent and three lymphocytes in the spinal fluid. The Queckenstedt test showed no subarachnoid block.

Iodized oil was injected into the cistern, and in the region of the third lumbar vertebra a small constant lateral filling defect was seen (Fig. 4) corresponding to the appearance reported in cases of localized extradural masses encroaching on the spinal canal.[2, 3]

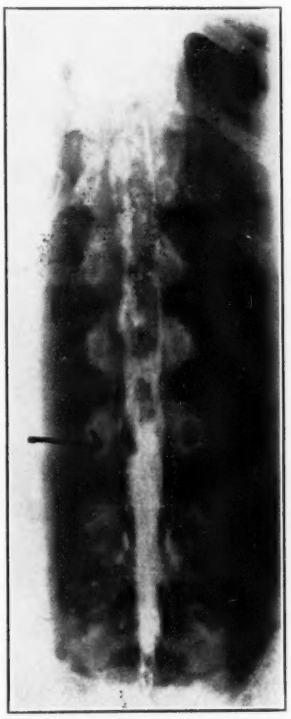

Fig. 4.—Case 2. Lipiodol injection (cistern) showing a small irregularity at L3 vertebral level (arrow) consistent with an extradural lesion.

Laminectomy on May 31, 1937 (Dr. William Hill), revealed, at the level of the third lumbar vertebra, a dense yellow ligamentous band running transversely across the dura. Above this area there was a bulging of the epidural fat. The constricting band was divided, dissected back on either side and excised. The dura and arachnoid were then opened and the lipiodol removed. There was no evidence of tumor and no projection into the canal in the region of the intervertebral disk.

Microscopic examination of the removed tissue showed a typical ligamentous structure consisting of uniformly dense fibrous tissue, containing few cells (Fig. 5).

The patient made an uneventful convalescence. He was discharged thirteen days postoperatively with the wound well healed. There was no essential change from his preoperative neurological status.

The patient reported two months after operation. He had experienced slight improvement. Examination showed no neurological abnormalities above the pelvis, except diminished left abdominal reflexes. The motor power of the legs, knees, and hips was fairly good, the patient being able to walk quite well without a cane. There was almost complete bilateral footdrop. Skin sensation was intact throughout. Position sense was normal, but vibratory sense was greatly diminished in each foot. There was no sphincter disturbance. The knee jerk was absent on the left and markedly diminished on the right. No ankle jerks were elicited. In the Romberg position the patient swayed markedly, probably because of poor control of the feet. Dorsiflexion of the feet was impossible.

When last seen, about seven months after operation, his condition was essentially unchanged as compared with his condition five months previously. The patient stated that, although his disability had been steadily progressive before the operation, it has been stationary since. He was referred to the Orthopedic Department for treatment of the footdrop.

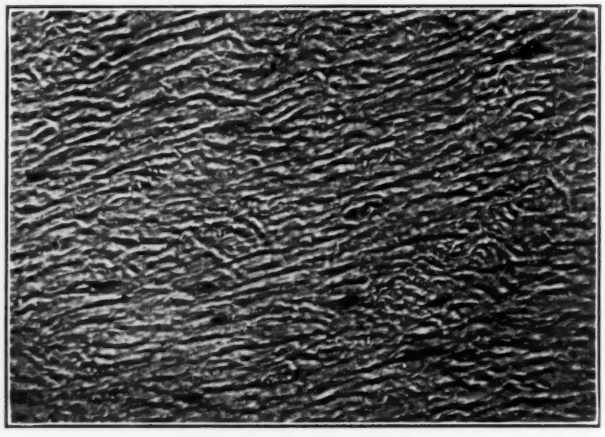

Fig. 5.—Case 2. Photomicrograph of lesion removed at operation. Typical fibroelastic structure of ligamentum flavum (×600).

COMMENT

The two cases here presented are atypical as compared with the justifiable generalizations of Spurling and his colleagues[1] based on the manifestations of previously observed cases. (For summary of typical findings in other cases see Table I.) In Case 1 the location of the lesion in the thoracic region is unique, inasmuch as in all other cases, including Case 2 of this report, the lesions occurred in the lumbar or lumbosacral region. Case 1, in addition, after an apparent operative cure, showed a complete return of disability and was found to have a similar lesion at a level one vertebra above the original site. The recurrence in this area was associated with a marked extradural development of tuberculous granulation tissue, although sections of the original lesion revealed no evidence of inflammation (Fig. 2). In no previous case has recurrence

TABLE I

SUMMARY OF 23 TYPICAL CASES RECORDED IN THE LITERATURE TO DATE (INCLUDING 2 CASES FROM THIS CLINIC) TO SHOW SIMILARITY OF FINDINGS*

Age.—	
Extremes	16-59 yr.
Average	36.6 yr (22 cases)
Sex.—	
Male	18 cases
Female	5 cases
History of Trauma.—	
Direct	1 case
Indirect	15 cases
No history	7 cases
Symptoms.—	
Pain in back or legs	23 cases
Weakness of legs	12 cases
Sphincter disturbance	1 case
Impotence	3 cases
Signs.—	
Hyperesthesia	14 cases
Hypesthesia	15 cases
Anesthesia	7 cases
Motor weakness	14 cases
Absent or diminished ankle jerks	15 cases
Atrophy	6 cases
Queckenstedt Test.—	
Normal	15 cases
Block demonstrated	3 cases
Not done or not recorded	5 cases
Spinal Fluid Protein.—	
Normal	2 cases
Elevated (above 45 mg. per cent)	13 cases
Not recorded	8 cases
Lipiodol.—	
Defect or block	18 cases
Not reported or not done	5 cases
Location.—	
Lumbar spine	17 cases
Lumbosacral spine	6 cases
Postoperative Course.—	
Relieved	19 cases
Slight residual pain or weakness	2 cases
Recurrence	1 case
Postoperative deaths (meningitis)	1 case

*Elsberg,[6] 1 case; Towne and Reichert,[5] 2 cases; Puusepp,[7] 3 cases; Abbott,[8] 1 case; Spurling, Mayfield, and Rogers,[1] 7 cases; Brown,[9] 7 cases; Meredith and Lehman (*see* Supplementary Note), 2 cases.

of symptoms been noted* and in none has tuberculous granuloma, or, in fact, any inflammatory tissue, been found.

There is no question that the mechanical conditions found in the cases reported elsewhere were present in Case 1 of this report, including direct evidence of subarachnoid block and an increased spinal fluid globulin. When the lesion was first uncovered, it resembled in detail the lesion described by Towne and Reichert,[5] and when it was removed not only was the mark of constriction obvious, but removal was followed

*Spurling[1] reports mild recurrence of pain in one case after the date of publication of his paper.[1]

by practically complete, although not permanent, recovery. Furthermore, the histologic picture, except for slight evidence of perivascular inflammation in the epidural fat, was comparable to the histologic picture illustrated in their paper and resembled closely the appearances seen in the study of a normal ligament (Fig. 2). In other words, except for the location, the pathology of the lesion in this case at the onset was identical with that of other reported cases. At the time of first discharge, there was no hesitation in making a definite diagnosis of hypertrophy of the ligamentum flavum.

The later findings led to some doubt as to the identity of this case with others reported, largely because of the definitely tuberculous nature of the tissue removed at the second operation. Variation from the typical neurological picture is explained here, of course, by the fact that the spinal cord rather than the cauda equina was subjected to compression.

The pathogenesis of the cases heretofore recorded is obscure, although trauma seems to play a part. The unusual behavior of this case (Case 1), particularly the appearance of tuberculous granulation tissue between the first and second operations and the positive blood Wassermann, offer confusing elements which in this case might be associated with the origin of the lesion under consideration. The relationship of syphilis or tuberculosis to this particular case must remain unsettled.

The striking variation in Case 2 from the typical manifestations of the disease lies in the neurological findings. As contrasted with all other cases, including Case 1 of this report, this patient was free from pain. The chief complaint and the neurological findings were almost entirely motor, consisting of muscle weakness, particularly in dorsiflexion of the feet. Although almost two-thirds of the typical cases reported (Table I) presented some motor weakness, it was in no case the presenting symptom and was always associated with marked afferent phenomena. The only sensory disturbance in this case was some loss of vibratory sense. Both gross and microscopic pathologic findings in the excised ligament were typical (Fig. 5), including the site of occurrence. In addition, the x-ray demonstration of a lateral defect in the shadow of the iodized oil corresponded exactly to the appearances reported in other cases. An elevated cerebrospinal fluid protein below the defect also suggested the typical mechanical derangement.

The failure to obtain neurological relief following the surgical removal of the ligament also makes Case 2 unusual. It is possible that an undiscovered cause for the muscle weakness might still be present. It seems unnecessary, however, to make such an assumption in the presence of a known lesion which could be responsible for neurological changes in the motor nerves involved. It is probable that this case represents hyper-

trophy of the ligamentum flavum with atypical neurological findings. If so, it also represents an important addition to our knowledge of this unusual condition.

The atypical site, course, and neurological behavior illustrated by the two cases herein reported suggest that knowledge of hypertrophy of the ligamentum flavum is yet too undeveloped to enable one to place entire reliance on the rather characteristic picture heretofore described. It is desirable that all unusual instances of the disease be reported in detail. It is only on the basis of a much larger series of cases that a final perspective of this condition can be obtained.

SUPPLEMENTARY NOTE

The following two cases of the typical syndrome of hypertrophy of the ligamentum flavum, as described by previous observers, have been seen during the past year in this Clinic. These are here reported not only as a contrast to the cases recorded above, but also to complete the literature of a rare condition.

CASE 1.—White adult, aged 37 years, male. Pain in the right hip, thigh, and leg of six months' duration. No direct trauma to back; patient is a truck driver. Lost seven pounds of weight in four weeks before admission. Totally incapacitated for work.

Examination: Ankle jerks unobtainable. No numbness to pinprick. Atrophy of muscles in right calf. Lumbar curve kyphotic. No muscle weakness.

Queckenstedt (L_{4-5}) normal. Fluid faintly xanthochromic. Spinal fluid protein: 100 mg. per cent; 4.5 c.c. descending lipiodol showed typical defect in oil column at L_{4-5} interspace on right side. Laminectomy (L_4 to S_1): Hypertrophied ligamentum flavum found and removed (7 mm. thick). Microscopically verified. Uneventful recovery. Follow-up examination (two months after operation): much improved. Gained eleven pounds in weight. Severe pain in right hip and leg has disappeared. Gait erect and brisk. Back at work as a truck driver.

CASE 2.—Colored adult, aged 42 years, male. Pain in lower back and left leg, intermittently, for three years. Four months before admission had sudden pain in back while lifting a heavy log. Patient is a day laborer. Excessive use of sedatives. Totally incapacitated for work.

Examination: Ankle jerks unobtainable. Hyperesthesia to pinprick in left thigh, hip, and leg. Atrophy of left calf. Severe pain on palpation of left sciatic nerve in thigh. No weakness of legs or footdrop. No incontinence.

Queckenstedt (L_{3-4}): slight subarachnoid block. Slight xanthochromia. Spinal fluid protein: 225 mg. per cent. Blood Wassermann four plus. Five cubic centimeters lipiodol (descending) showed typical defect at L_5 to S_1 interspace on left side. Laminectomy (L_5 to S_1): hypertrophied ligamentum flavum found and removed (1.0 cm. thick). Microscopically verified. Uneventful recovery. Follow-up examination (seven weeks after operation): complete arrest of symptoms.

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SUBCUTANEOUS INJURIES OF THE INTESTINE AND MESENTERY

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THE subject of subcutaneous injuries of the abdominal viscera is assuming major importance in the list of acute surgical emergencies because of the rapidly increasing number of automobile accidents.

This paper proposes to deal with those cases of trauma in which paramount injury was sustained by the intestine or its mesentery. Special emphasis will be placed upon a discussion of those factors which influence the mortality rate. However, for a clear understanding of the subject, it is necessary to consider the mechanism of injury and the signs and symptoms which are important in diagnosis.

This report is based upon an analysis of 25 cases of perforation of the intestine or tear of the mesentery from the surgical wards of the Los Angeles County Hospital Unit 1. In this series there were 14 deaths, a mortality of 56 per cent. The fatal group included 9 cases that were not operated upon. There were 5 deaths in the 16 operative cases, a mortality of 31 per cent.

The trauma responsible for this type of injury may be direct violence, indirect violence, or muscular action.[14] The greatest number are probably due to direct violence which may be subdivided into generalized or local trauma. According to the classification of Moty,[11] there are three modes of rupture: (1) The intestine (or its mesentery) may be crushed. (2) The intestine (or its mesentery) may be torn. (3) The intestine may burst because of pressure within its lumen.

In crushing injuries compression may be accomplished by one vulnerating body when an intestinal coil is caught between the traumatizing object and the vertebral column, or the abdomen may be compressed between two objects. When traction is made upon the intestine and mesentery by the application of force at a tangent with the abdominal wall, a tearing injury will result. Explosive or bursting ruptures occur from sudden rise of pressure within the lumen of the intestine when the pressure exceeds the limit of elasticity of the intestinal wall.

According to John,[7] rupture may occur by indirect violence when a person falls, landing on his feet or buttocks with the trunk in an upright position so that the sudden stop causes the intestine, by its own weight, to jerk violently against its mesenteric attachment and so cause tearing.

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Muscular effort alone, as a cause of intestinal rupture, is the subject of an article by Wilensky and Kaufman.[16] They call attention to the high incidence of hernias in the series of cases they report gathered from the literature. It seems evident that the frequency of hernia in this type of bowel rupture is quite significant. Aird,[1] likewise, stresses the importance of hernias associated with subcutaneous intestinal rupture. He states that rupture may be due to violence applied directly to the hernia, to direct abdominal injury, or, more rarely, to violent hyperextension of the trunk. Vance[15] believes that the hernia sac aids the production of this lesion because the coverings of the sac are too weak to support the intestinal wall against the explosive force within its lumen.

SYMPTOMS AND SIGNS

The price of early diagnosis must be constant alertness to suspect intra-abdominal injury in the presence of severe general trauma, whether or not there is a history of direct abdominal trauma.

The clinical picture in the early stages when the trauma has been severe, especially with associated extra-abdominal injuries, is one of shock. Extra-abdominal injuries with severe shock overshadowed the abdominal injury and caused diagnostic error in four cases in this series. On the other hand, as Cooke states:[4] "In the presence of slight general trauma, rupture of the intestine may produce few immediate symptoms."

Occasionally, delay in onset of symptoms may be due to secondary perforation of the bowel, the original lesion at the time of accident being a bruise of the intestinal wall, which later sloughs with the onset of symptoms of perforation. In one case in this series contusion of the bowel wall was sufficient to devitalize the tissue to the extent that it became permeable to the passage of bacteria with the development of generalized peritonitis.

A careful consideration of the history with reference to the type of injury sustained, together with a careful physical examination and close observation over a period of three or four hours, will lead, at least, to a definite suspicion of intra-abdominal injury which is adequate justification for operation.

It is remarkable that, even in the presence of extreme violence, there is usually little evidence of injury to the abdominal parietes. There was evidence of trauma to the abdominal wall in only 8 of 25 cases. Abrasions and bruises were the most common injuries. The only instance in this series of severe injury was a case of traumatic hernia, in which all layers of the abdominal wall were ruptured except the skin.

Evidence of injury to abdominal parietes in 25 cases of intestinal and mesenteric injury:

1. Abrasion across upper abdomen and lower ribs	1 case
2. Imprint of horseshoe above symphysis on right side	1 case
3. Abrasion of skin over splenic area	1 case
4. Bruise in left upper quadrant (imprint of 2-inch pipe)	1 case
5. Traumatic hernia of left lower quadrant, size of orange	1 case
6. Superficial abrasion along right costal margin	1 case
7. Abrasion of lower abdomen	1 case
8. Abrasion above umbilicus	1 case

PAIN

Pain is present to a degree in all cases. When constant and increasing in severity, it is the most reliable symptom in diagnosis. Pain was recorded as severe or intense in 11 instances, moderate in 9, and slight in 2. In 3 patients that were moribund on admission, the presence or absence of pain was not recorded. In 3 cases of mesenteric injury, associated with much free blood in the peritoneal cavity, shoulder pain was present.

TENDERNESS AND RIGIDITY

The presence of tenderness and rigidity in this series was quite constant. Tenderness, as a rule, is quite diffuse, with frequently a localized area of maximum intensity over the site of injury. Without escape of intestinal contents or intraperitoneal hemorrhage, the tenderness may be quite moderate and well localized.

Tenderness of the pelvic peritoneum, demonstrated by rectal examination, is an important diagnostic sign, indicating, in early cases, the presence of blood, or rarely, free intestinal contents. Later it may indicate the extension of peritonitis to the pelvis.

Although in the rare exception, rigidity may be absent; it may be safely stated that this symptom is the most constant and valuable physical sign in the examination of the abdomen. Like tenderness, it is more often generalized, with a local area of maximum intensity. Absence of muscular rigidity may be found in those cases of contusion of the bowel without primary rupture or hemorrhage, occasionally in cases with profound shock, and rarely in late cases with well-developed peritonitis and profound toxemia in which meteorism predominates.

Cases with generalized rigidity	20
Cases with local rigidity only	2
Cases without rigidity	3

Cope[5] stresses the value of muscular rigidity as an important symptom, especially where it persists over a period of a few hours, as that due to simple contusion of the muscles tends to pass off within a comparatively short period of time.

VOMITING

Vomiting is significant, especially when repeated and continuous. However, it is not invariably present. It was absent in 3 cases in this series in which the trauma was localized and pathologic lesion was confined to the intestine. Moynihan[12] stated that vomiting, with a continuous increase of pulse rate after the period of shock is over, were two signs together which justified exploration.

SHIFTING DULLNESS

The presence of free fluid in the peritoneal cavity, as denoted by shifting dullness in the flanks, is a positive sign of intraperitoneal injury that calls for operative intervention. During the first few hours following rupture, contraction of the muscular coats of the intestinal wall usually prevents the escape of contents in an amount large enough to be detected by abdominal percussion except with large or complete tears. However, with tearing of mesenteric vessels or, more rarely, vessels in the bowel wall itself, bleeding sufficient to give dullness in the flanks will occur. There were 8 cases in which shifting dullness in the flanks was demonstrated. In 2 cases it was due to massive escape of intestinal contents from large tears of the bowel and in the remaining 6 it was due to hemorrhage from the mesentery, from the bowel wall, from a solid viscus, or from a combination of these sources.

Presence of shifting dullness	8 cases
Absence of shifting dullness	3 cases
No mention of shifting dullness	14 cases

COMPLETE ABSENCE OF AUDIBLE PERISTALSIS (SO-CALLED "SILENT ABDOMEN")

Too much reliance should not be placed on this sign. It is true, in the majority of cases, that audible peristalsis is absent following perforation of a hollow viscus, but in the occasional instance it may be present and even active. It is well to remember in this connection that audible peristalsis may be absent in the normal peritoneal cavity for a period of time which exceeds that ordinarily consumed in auscultation of the abdomen. In such cases, however, it may usually be elicited by mildly stimulating the abdominal wall by blunt stroking or pressure with quick release.

Audible peristalsis absent	8 cases
Audible peristalsis present	1 case
Audible peristalsis not mentioned	16 cases

CLAYBROOK'S SIGN

The transmission of the heart and respiratory sounds so that they can be heard almost as well all over the abdomen as over the chest

was first described by G. A. Peters of Toronto in a paper entitled "The Telephonic Properties of the Inflamed Abdomen" in the *Canadian Journal of Medicine and Surgery*, December, 1902. It was reported again by Claybrook[3] in 1904. The latter author considered it a positive indication for laparotomy whether other signs are present or not and believed it due to irritation of the parietal peritoneum by the sudden outpouring of foreign material into the abdominal cavity. He noted the sign in cases of ruptured solid viscus with hemorrhage as well as in cases of ruptured hollow viscus with free air. Ledgard[8] believed the phenomenon was due to gas in the peritoneal cavity as he did not think the presence of free fluid alone was enough to produce the sign. I, however, have observed the sign in the case of rupture of solid as well as hollow viscus, but I am not prepared to venture an opinion as to its value as a frequent diagnostic sign.

OBLITERATION OF LIVER DULLNESS

Diminution or obliteration of liver dullness is not a frequent sign of early perforation of the intestine. Certainly it is not found as frequently in traumatic rupture of the bowel as in acute perforation of peptic ulcer. Absence of liver dullness may indicate a late stage of peritonitis' being caused by ileus and, consequently, in such instances, is a bad prognostic sign. In this series obliteration of liver dullness was found in 2 cases, 1 of which was due to tympany from distended bowel in a well-advanced peritonitis.

X-RAY

Positive findings in the flat x-ray plate of the abdomen are diagnostic. The presence of free air, intestinal contents, and blood may be demonstrated by this method. As a positive finding its value is obvious, but negative findings should not influence one's decision. Only 1 case in this group, a rupture of the jejunum, was x-rayed with reference to the demonstration of free air. The findings were negative. Greater use should be made of this valuable diagnostic method in doubtful cases for, although the percentage in which free air will be demonstrated is probably small, yet those in which free intestinal contents and blood may be shown will raise the number with positive x-ray findings considerably.

TEMPERATURE AND PULSE

During the initial period of shock, a subnormal temperature and weak thready pulse are to be expected. Following this period, these two indicators are not a reliable guide as they are apt to be normal. However, an abnormality consisting of a gradual but steady increase in pulse rate and temperature is considered of great diagnostic importance. Unfortunately, these are comparatively late signs and to wait for them

may be to wait until the pathologic process has progressed too far. Following the period of shock, a steadily increasing pulse rate with a falling blood pressure is indicative of hemorrhage.

THE BLOOD COUNT

Because of the associated shock with a depletion in plasma volume, the red cell count in the early hours of bowel perforation will tend to be normal, even with considerable hemorrhage. The leucocyte count is characteristically elevated in part because of decrease in plasma volume and in part because of stimulation to the peritoneum. The red cell count, taken in 7 cases, ranged from 2,600,000 to 5,500,000 with 6 well above 4,000,000. The low count occurred in a case of extreme retroperitoneal and intraperitoneal hemorrhage associated with a fractured pelvis. Leucocytosis was found in all except 1 of 14 cases, ranging from 6,800 to 32,200, the latter occurring in a case of ruptured mesentery without other injury.

Emphysema of the posterior abdominal wall is a diagnostic sign of retroperitoneal rupture of the duodenum or colon. Butler[2] calls attention to the fact that emphysema of the pelvic cellular tissues may be palpated on rectal examination. In this series the sign was not observed.

FACTORS WHICH INFLUENCE THE MORTALITY RATE*

Nature of the Traumatizing Force.—Automobile accidents were responsible for 17 cases, with a mortality of 65 per cent. The remaining 8, with a mortality of 37 per cent, were due to a variety of accidents, but with a common factor, 1 case excepted, of well-localized trauma applied to the abdomen. The one exception occurred in a patient who jumped from a window, presumably in which case the violence was indirect.

The high mortality rate in the group caused by motor car accidents is due to the greater degree of violence and its wider application with serious associated injuries. There were 9 instances of associated extraperitoneal injury and 2 of intraperitoneal injury, all of which occurred in those due to automobile accidents. There were 3 instances of automobile injuries in which the trauma was localized, due to the steering wheel striking the abdomen.

Location of Intestinal Perforation.—The ileum was the site of perforation in 10 cases, with a mortality of 20 per cent. Seven were unassociated with other injury, not including the mesentery. Six were due to localized trauma. There were 5 cases of perforation of the jejunum with 3 deaths, a mortality of 60 per cent. Two cases of rupture of the duodenum and 1 case of rupture of the descending colon were fatal.

*See Table I.

Laceration of the Mesentery.—When a tear of the mesentery occurs with bleeding of any considerable quantity, the specific sign of free intraperitoneal fluid, shifting dullness in the flanks, is present. Eleven of 12 cases of mesenteric tear were due to automobile accidents. The 1 exception was that due to indirect violence. Five of these 12 were associated with intestinal perforation. Of the remaining 7, 1 was associated with severe bruising, but not rupture of the bowel wall. In this group of 7, unassociated with bowel rupture, only 1 was operated upon. This case was unassociated with any other injury and recovery took place. All of the remaining 6 died. They were all associated with other injuries. Four were complicated by fractures; 1, by rupture of the liver and kidney; and 1, by severe bruising of the bowel wall. The reason for not operating upon these 6 patients was because of diagnostic error in 3 and moribund condition of the patient in 3. The cause of death in each case was due, essentially, to hemorrhage, although shock was a contributing factor in 2 and peritonitis in 2.

It should be remembered that the danger of mesenteric tears is twofold. Hemorrhage is probably the most frequent cause of death. However, fatal peritonitis may result from devitalization or sloughing of the bowel wall deprived of adequate blood supply. A rare but highly fatal complication is "mesenteric disinsertion," or complete tearing of the mesentery from the bowel for variable distance. This condition, as well as mesenteric injuries of lesser magnitude in which the viability of the bowel is jeopardized, necessitates intestinal resection.

Associated Intraperitoneal Injury.—There were only 2 cases of associated intraperitoneal injury; a rupture of the liver (and kidney) occurred in a case of torn mesentery and a ruptured pancreas occurred with a rupture of the duodenum.

Associated Extraperitoneal Injury.—This group is instructive. There were 8 cases, 7 of which were fractures. Six of these were not operated upon, 3 because of erroneous diagnoses and 3 because of moribund condition of patient on admission. Four of these fracture cases occurred with mesenteric injuries, without intestinal rupture.

This group forms an important one. Because of the increased number of automobile accidents, the relative and actual incidence of these cases is becoming greater. They are poor surgical risks because of shock and hemorrhage. Hemorrhage from a large mesenteric vessel may be rapidly fatal, especially when combined with shock from a major fracture. The diagnosis may be masked by an obvious injury, while the intra-abdominal pathology is overlooked even with severe intraperitoneal hemorrhage. This chance is increased by the fact that evidence of abdominal trauma in the form of abrasions or other evidence of external injury may be, and usually is, quite insignificant.

In order that these cases may not be overlooked, abdominal injury should be suspected in every case of severe general trauma, whether or

TABLE I

	SEX	AGE	NATURE OF TRAUMATIZING FORCE	LOCATION OF INTESTINAL RUPTURE	TEAR OF MESENTERY	ASSOCIATED INTRAPERITONEAL INJURY	ASSOCIATED EXTRAPERITONEAL INJURY	NUMBER OF INTESTINAL RUPTURES	DURATION OF INJURY BEFORE OPERATION	REASON CASE WAS NOT OPERATED UPON	RESULT
Intestinal and Mesenteric Injuries Due to Automobile Accidents											
1.	M	12	Caught between automobile bumpers	–	×	–	–	–	7½ hr.	–	Recovery
2.	M	36	Struck by automobile	–	×	Rupture kidney and liver	–	–	–	Diagnostic error	Death, hemorrhage
3.	M	45	Struck by automobile	Ileum	–	–	Retroperitoneal hemorrhage; fracture, pelvis	1	–	Moribund	Death, shock
4.	M	28	Steering wheel struck mid-abdomen	Ileum	×	–	Fracture, transverse process lumbar vertebrae	1	15 hr.	–	Recovery
5.	M	32	Struck by automobile	Bruise of bowel only	×	–	–	–	–	Moribund	Death, hemorrhage and peritonitis
6.	M	63	Struck by automobile	–	×	–	Fracture, pelvis	–	–	Diagnostic error	Death, hemorrhage and shock

TABLE I—CONT'D

7.	M	29	Automobile accident	–	×	–	Fracture, femur	–	–	Moribund	Death, hemorrhage
8.	M	26	Automobile accident	–	×	–	Fracture, skull and 3rd to 8th ribs	–	-	Moribund	Death, hemorrhage and shock
9.	M	18	On motorcycle struck by automobile	Ileum	–	–	Traumatic hernia	1	6 hr.	–	Recovery
10.	M	26	Steering wheel struck mid-abdomen	Jejunum	–	–	–	1	5½ hr.	–	Recovery
11.	M	19	Automobile accident	Duodenum	–	–	–	2	1 wk.	–	Death, peritonitis
12.	M	26	On motorcycle struck by truck	Jejunum	–	–	Fracture, femur	1	–	Diagnostic error	Death, peritonitis
13.	M	43	Steering wheel struck abdomen	Jejunum	–	–	–	1	7 hr.	–	Recovery
14.	Fe	32	Automobile accident	Jejunum	×	–	-	1	14 hr.	–	Death, hemorrhage and peritonitis
15.	M	19	Knocked off moving automobile	–	×	–	Fracture, scapula	–	–	Diagnostic error	Death, hemorrhage and peritonitis
16.	Fe	28	In bus struck by milk truck	Ileum	×	–	–	1	4 hr.	–	Recovery
17.	M	27	Automobile accident	Duodenum	–	Pancreatic rupture	–	1	5 hr.	–	Death, peritonitis

TABLE I—CONT'D

	SEX	AGE	NATURE OF TRAUMATIZING FORCE	LOCATION OF INTESTINAL RUPTURE	TEAR OF MESENTERY	ASSOCIATED INTRAPERITONEAL INJURY	ASSOCIATED EXTRAPERITONEAL INJURY	NUMBER OF INTESTINAL RUPTURES	DURATION OF INJURY BEFORE OPERATION	REASON CASE WAS NOT OPERATED UPON	RESULT
Intestinal and Mesenteric Injuries Due to Miscellaneous Causes											
1.	M	5	Pinned to wall by trailer tongue	Ileum	×	–	–	1	6 hr.	–	Recovery
2.	M	18	Fall, abdomen striking plank edge	Ileum	–	–	–	1	5½ hr.	–	Recovery
3.	M	74	Kicked in abdomen by horse	Ileum	–	–	–	1	5¾ hr.	–	Recovery
4.	M	62	Bale of hay struck hernia (truss)	Jejunum	–	–	–	1	8 hr.	–	Death, peritonitis
5.	M	37	Fall into water, abdomen striking floating pole	Ileum	–	–	–	2	25 hr.	–	Death, peritonitis
6.	M	8	Fall, striking abdomen on end of metal pipe	Ileum	–	–	–	1	7½ hr.	–	Recovery
7.	M	40	Jumped from window	Descending colon	×	–	–	1	–	Moribund	Death, peritonitis
8.	M	30	Struck in abdomen by fist	Ileum	–	–	–	1	10 hr.	–	Recovery

not there is external evidence or history of trauma directly to the abdomen. Examination of the abdomen for tenderness, rigidity, and especially evidence of free fluid, should be painstaking. Prompt and adequate treatment of shock is essential, for these cases constitute desperate risks and a lethal outcome will result unless shock and hemorrhage are combated promptly to improve the patient's condition sufficiently to permit operation.

Of 18 cases of bowel rupture, the perforations were single except in 2 cases. There were 2 in this group that were not operated upon because the patients were in extremis.

DURATION OF INJURY BEFORE OPERATION

The importance of early diagnosis and prompt treatment is well illustrated in this group of cases. Ten patients operated upon within eight hours gave a mortality of 10 per cent. Six were operated upon after eight hours with a mortality of 66 per cent. Nine cases without operation died. According to Lockwood,[9] the best results follow operation between two to four hours after injury, the mortality rate increasing approximately 15 per cent every four hours thereafter.

SIEGEL'S STATISTICS (SENN[13])

		MORTALITY
Cases operated upon during	first 4 hours	15.2%
Cases operated upon	5 to 8 hours	44.4%
Cases operated upon	9 to 12 hours	63.6%
Cases operated upon later		70.0%

Massie,[10] on the other hand, reporting 31 cases operated upon with a mortality of 78 per cent, did not believe the time factor to be of such great importance.

TREATMENT

Even though shock is not present at onset, it may occur during the operative procedure and this event should be anticipated. Restoration of the blood volume should be promptly instituted. In this series blood transfusions were used in 11 cases and 6 per cent gum acacia, an adequate emergency substitute, in a lesser number. The facility with which transfusions of blood are given in this institution obviates, to a large extent, the necessity for the use of acacia except in extreme cases. Hemorrhage is treated in conjunction with shock and by operation not too long delayed. Peritonitis, a complication of delayed treatment, can be prevented by early operation. Operation should be undertaken within a period of four or five hours after injury. This gives ample time to treat shock if such treatment is to avail and is early enough to avoid the onset of peritonitis. As far as the operative procedure is concerned, intestinal resections are to be avoided if simple closure of the perforation and repair of the mesentery will suffice.

Intraperitoneal drainage should be the rule except in early cases. Four early cases in this series were closed without drainage and recovered. Limited areas of the bowel wall which are severely bruised or otherwise traumatized without actual perforation should be carefully repaired or covered with omentum to prevent the possible catastrophe of late or secondary perforation.

Enterostomy may be indicated, as Counseller[6] advises in writing on gunshot wounds of the bowel, for the purpose of relieving tension on the suture line in all cases of multiple perforations. An enterostomy was performed in 1 case of perforated ileum of twenty-five hours' duration. Death occurred from generalized peritonitis.

The cases in this series that were operated upon early and recovered were remarkably free of postoperative complications.

SUMMARY AND CONCLUSIONS

1. The mechanism of intestinal and mesenteric injuries is described.

2. The importance of careful abdominal examination in traumatic injuries is stressed. Attention is called to the fact that usually little evidence of external injury to the abdominal wall will be found.

3. Symptoms and signs are described with special reference to abdominal pain, tenderness, rigidity, evidence of intraperitoneal fluid, vomiting, and the pulse and temperature.

4. Factors which influence the mortality rate are considered with reference to: (A) the nature of the traumatizing force, (B) location of the intestinal perforation, (C) mesenteric tears with special reference to the frequency and high mortality of those unassociated with bowel rupture, (D) associated injuries, and (E) duration of the injury before operation.

5. The treatment of shock is emphasized.

6. It is believed that the optimum time for operation is from two to five hours after injury.

7. Operation is indicated when a reasonable suspicion of intraperitoneal injury exists based upon the symptoms and signs enumerated whether or not there is evidence of external abdominal trauma or a history of direct abdominal violence.

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Editorial

Gas Bacillus Infection

GAS bacillus infection can be prevented; with the recent methods offered, not only will many lives be saved, but many limbs as well

In gas bacillus infection the etiologic agent, the *Cl. welchii* group, and the predisposing factor, trauma, are absolutely interdependent. These anaerobes constitute a large group of bacilli, widely distributed in nature and composed of saprophytic and pathogenic organisms. *Cl. welchii* (Welch and Nutall), *Vibrion septique* (Pasteur), and *Cl. oedematiens* (Weinberg and Séguin) are the more important pathogens commonly associated with this disease. In this country *Cl. welchii* is the most common causative agent.

Deep penetrating wounds with destruction of muscle and liberation of carbohydrates form ideal growth conditions for these organisms, and because of this, the incidence is highest in compound fractures. Next in order of frequency are the penetrating injuries to soft parts, especially those incurred by shotgun. Statistics obtained during the World War reveal that five times as many compound fractures are complicated with this infection as are injuries to the soft parts.

In civil practice, auto and train accidents, especially those occurring in rural sections, carry the greatest incidence of infection. Shotgun is another great instrument of trauma, the wounds of which are frequently complicated with anaerobic infections. Gage has cultured *Cl. welchii* from the wool wadding of shotgun shell in every attempt.

The lesion is primarily a local one, but systemic reactions occur rapidly, especially in the fulminating cases. When infection occurs, the muscle at first assumes a brick red color resembling cooked meat. It soon softens, becomes diffluent, and changes in color to a green, brown, or black. Gas is formed and forces itself up and down the muscle bundles, opening up new fields for infection. The gas, according to Thorek, is the result of fermentation of isomaltose and dextrose converted from the glycogen of the living muscle. Taylor and Manson have demonstrated that this gas may develop high pressure. In two hours the pressure rises and in six hours a pressure of 23 pounds has been obtained. Thus more muscle is destroyed by impairing its blood supply, either by air emboli or pressure. Even the main trunk may be occluded, especially if the wound is closed or enclosed in a rigid cast.

Powerful exotoxins are produced and clinically there are three toxins: a local necrotizing toxin, producing necrosis of muscles; a hemolytic

toxin, causing a severe anemia; and, finally, a pure systemic toxin. The last two may easily be the result of a single toxin.

The following clinicopathologic classification is suggested, dependent upon the relative degree of the various toxins present, the extent of the local pathology, and the relation of the lesion to the severity of the systemic toxemia:

1. *Primarily Toxic (Fulminating).*—Toxemia far out of proportion to local lesion.

2. *Primarily Gangrenous (Mechanical).*—Local lesion out of proportion to systemic toxemia.

3. *Usual or Common.*—Toxemia in proportion to local lesion.

4. *Localized or Delayed.*—Lesion and toxemia relatively mild.

The fulminating case is quite classical and usually offers no diagnostic difficulty. The patient is in a state of profound shock with a rapid, thready pulse, low blood pressure, a delirious state, and temperature which varies from 103 to 105°. The respirations are rapid and frequently labored and characteristically there is a marked anemia present. Following traumatic injuries, the recognition is immediate, but as a complication in the clean postoperative case the surgeon is frequently confused. In the latter instance an erroneous impression of occult bleeding is likely to be had.

The primarily gangrenous type due to mechanical occlusion of the main vessels is characterized by a mortified and gaseous extremity which is clinically obvious. In these cases the toxemia is relatively mild because of the lack of absorption due to venous compression.

The usual, or common, variety occurs in neglected open or partially open wounds of 24 or 48 hours' duration. The gas is not so destructive as it never develops much pressure, but escapes through the open wound. The exudate is likewise discharged rather than absorbed. The degree of toxicity is usually proportionate to the extent of the local lesion; however, this is not a strict rule.

The localized or delayed type occurs in old wounds. The lesion is well walled off and the offending agents are of low virulence. Such conditions are usually discovered by incision, culture, or x-ray.

Diagnosis in gas bacillus infection is relatively easy and the detection of early cases is not difficult if the disease is kept in mind. All potentially infected wounds should be scrupulously examined, not daily, but every four or five hours. The onset of gas infection can be detected before the systemic symptoms are manifested in all except the extremely fulminating cases. Pain of a severe degree and out of proportion to the size of the lesion is considered the earliest constant finding. One should not wait for the appearance of systemic manifestations, such as agonizing pain, rapid thready pulse, high temperature, restlessness, prostration, and apprehension. Exquisite pain on pressure, edema, and diffuse reddening about the wound are early findings. Slight pressure will

express a thin watery or sanguinous fluid with or without a few bubbles of gas. A direct smear will reveal gram-positive, encapsulated, nonmotile bacilli with staphylococci and streptococci, which is diagnostic.

In the past such diagnostic criteria may have seemed inconclusive for the institution of therapy, especially when amputation was resorted to immediately. But in this day of less radical methods, such findings are absolutely adequate. If a diagnosis is not confirmed by culture, no harm has been done. The lesion was correctly treated as an infected wound with the addition of other more specific measures.

The use of x-ray in the diagnosis has received too little attention. In deep-seated wounds, careful successive examinations have proved it of value.

Gas bacillus infection has always carried a greater mortality rate than practically any other infection. The American Expeditionary Forces in France had a mortality of 48.5 per cent from this infection. In the postwar period two definite reductions were obtained. Immediately following the World War, the primary reduction was undoubtedly dependent upon the improvement of surgical methods. The second reduction occurred with the universal use of polyvalent antitoxin. Recently, with the valuable work of Kelly and others on the therapeutic use of x-ray, an even greater reduction in death rate is obtained. In his group of collective cases the mortality rate ranged from 5 to 10 per cent, depending on the type of case. The author, in collaboration with R. W. Cooper, reported twenty cases treated in a similar manner with mortality of 10 per cent.

The primary aim in treatment is to prevent the development of the disease. In no other phase of surgery is prophylaxis more important than in treatment of traumatic injuries. The immediate and proper care of wounds in general is the chief factor in reducing the incidence of gas bacillus infection. Under general anesthesia the field should be carefully prepared and a complete débridement performed. Muscle should be excised until it bleeds freely and contracts. If the surgeon is positive that the débridement is complete, he may close the wound tightly. If there is any doubt, the wound should be left open. A drain should never be used as it permits an entrance for organisms into the wound, as well as an exit for the collected secretions. In compound fractures the wound is treated in a similar manner, but in addition small fragments of bone are removed and contaminated edges of the larger fragments are excised with rongeurs. Interlocking of fragments with slight manipulation is often possible, especially in oblique fractures. In most compound fractures it is wiser to leave the wound wide open.

Prophylactic antitoxin given early, and in adequate dosage, is a definite preventative measure. The use of the x-ray prophylactically is

a recent valuable development. We have treated eight definitely contaminated wounds with no occurrence of the disease, but such a small series is of no significance.

The treatment of a developed case requires prompt and adequate surgical methods. The progress of the infection must be stopped and the symptoms must be relieved. These patients are invariably poor operative risks, and the severity of the toxemia should determine the degree of radicalism. The radical methods used so frequently in the past have claimed many lives unnecessarily. With the institution of "less radical" methods, antitoxin, and the x-ray, most of these patients could have been saved. Conservatism plays no part in the treatment of this disease. The methods advocated are decompression and débridement. Adequate decompression will prevent the progress of the destructive gas. Débridement means the excision of local lesion, especially the necrotic muscle. Surgery must be more extensive than the lesion, and muscle should be excised until there is a good blood supply and contractility is present. The wound is left wide open and irrigated with hydrogen peroxide. The latter is superior to all other fluids in the treatment of gas bacillus infection because of the liberation of nascent oxygen.

In cases of mechanical obstruction in which there is little toxemia, amputation can be accomplished quite safely following the usual preoperative supportive measures.

The use of serum therapeutically is still under discussion, but most of the reports indicate its value. There are two plausible explanations for its inefficiency in certain cases; either the serum was given late, and not in adequate doses, or the serum was monovalent or bivalent and not polyvalent, which is essential.

Roentgen irradiation therapy is a valuable adjunct in the treatment of gas bacillus infections. The factors upon which the beneficial effects of the x-ray are dependent are not known, and although many hypothetical explanations have been offered, none have been proved.

Less radical methods, combined with adequate dosage of polyvalent antitoxin and the therapeutic x-ray, will cure the usual case with little sacrifice of tissue. Furthermore, in the extremely toxic cases, where amputation although indicated is incompatible with life, the application of these methods will control the infection, combat the toxemia, and thus improve the general condition so that the necessary surgery can be done safely later.

A critic may think that those interested in this work are too enthusiastic over a mortality rate based on so few cases. But when one witnesses the spectacular effect of the therapeutic x-ray in gas bacillus infection he will realize that its value is not overestimated, and that the method is well worthy of further study.

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Recent Advances in Surgery

Conducted by Alfred Blalock, M.D.

SALT BALANCE IN SURGICAL PATIENTS

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(Continued from the September issue.)

Treatment of Hypochloremia.—Hypochloremia may be prevented if the patient is under the observation of the physician at the onset of the loss of body salt. However, not infrequently the patient has lost an unknown amount of salt-containing fluids before he consults a physician, and in such instances the volume-for-volume rule cannot be applied.

There are several ways of approaching the problem of salt replacement in patients with hypochloremia. The method most commonly used in the past has been largely one of trial and error. That is, after the plasma chloride concentration has been determined, the clinician gives the amount of salt he thinks will probably be needed, and then again determines the plasma chloride level to see how accurately he has estimated the patient's requirements. This method has three faults. (1) If the plasma chloride concentration is checked too soon after the saline administration, a misleading value will be obtained. In the studies that we are about to report, an interval of at least 12 hours elapsed between the completion of saline administration and the plasma chloride determination in order to avoid any error in this regard. (2) If the salt need of the patient has been underestimated, valuable time will be lost in restoring the body chemistry and physiology to normal. (3) If an excessive amount of salt has been given to a sick patient, he is apt to retain the extra salt together with water and thus develop water-logging of his tissues. Excessive salt administration usually will not be shown by an abnormally high plasma chloride level, since, as has been already pointed out, the plasma chloride concentration can rarely be forced above normal by large doses of sodium chloride. Often in sick patients it cannot be raised even to the lower limits of normal. Hence, if the clinician uses only the plasma chloride level as an index of overdosage of salt, he is apt to be misled into forcing salt upon the patient who is not able at the time to attain a normal plasma chloride

level. The only ways of determining excessive salt intake are by weighing the patient daily and by determining the urinary excretion of salt, and at times even this latter index may fail.

In 1923, Haden and Orr[61] recommended the administration of 1 gm. of sodium chloride per kilogram of body weight as the initial dose of salt in the treatment of the toxemia of intestinal obstruction. At the time they failed to realize that the salt administered was used to replace the salt lost by vomiting, believing that the function of the sodium chloride was to neutralize a toxin in the body. Nevertheless theirs was the first attempt to place salt administration on a quantitative basis. More recently Orr[111] has recommended 250 to 500 c.c. of a 2.5 or 5 per cent solution of sodium chloride intravenously for patients with marked hypochloremia.

In 1937, Falconer and Lyall[12] made a definite advance toward placing sodium chloride administration on an accurate basis. They gave known amounts of salt to patients with hypochloremia and determined the resulting rise in the plasma chloride level. As a result of their studies, they concluded that "in hypochloraemia about 20 grammes (from 15 to 30 grammes) of salt are required on the average to raise the plasma chloride by 100 mg. per 100 ccm."

Early in our investigation[110, 112] of the salt requirements of surgical patients, two simple but fundamental principles became apparent. First, it seemed obvious that the salt needs of a child weighing 20 kg. must be quite different from those of an adult weighing three times that amount. Secondly, we reasoned that if one could determine what portion or per cent of the total body salt had been lost to produce a given degree of hypochloremia one could calculate accurately the amount of salt that must be given to restore the body chlorides to normal.

The total salt content of the body has been discussed earlier in this paper. It will be recalled that Sherman[13] estimates the chlorine content of the body to be 0.15 per cent of the body weight, or expressed in terms of sodium chloride, 0.248 per cent of the body weight. On this basis, there are 148.8 gm. of salt in a 60 kg. individual; whereas, in a 20 kg. child there are only 49.6 gm. of salt. Thus, it is apparent that variations in body weight must be taken into consideration in determining the salt requirement of patients with hypochloremia.

It has also been shown that as secretions containing chlorides are lost from the body there occurs an accompanying fall in the plasma chlorides. Several workers have shown that this decrease in the plasma chlorides is also associated with a fall in the salt content of the other body fluids and tissues. It is a well-established fact that the concentration of chlorides in the cerebrospinal fluid parallels that in the blood

serum.[8] Hayden and Orr,[74, 81] and Gatch, Trusler, and Ayers[28] showed that the decline in plasma chlorides was accompanied by a fall in the chloride concentration of liver and muscle tissues. The thorough work of White and Bridge[11] on dogs with experimental intestinal obstruction led them to the conclusions that chlorine is lost from the tissues in amounts directly proportional to the decrease in the chlorine content in the blood, and the total dechlorination of the body corresponds closely to the salt recovered in vomitus and urine.

All of these findings seem to warrant the assumption that the plasma chloride level is a satisfactory index of the chloride concentration throughout the body. Hence, if the plasma chlorides are 20 per cent below normal, it seems reasonable to assume that about 20 per cent of the body chlorides have been lost. On this basis, knowing the normal salt content of the body and the portion of it that has been lost as indicated by the plasma chloride level, one should be able to calculate the number of grams of salt that must be returned to the body to restore the body chlorides to normal. These concepts may be expressed in the form of simple equations as follows:

1. $\%$ of body salt lost $= \dfrac{\text{Normal pl. chl.} - \text{Actual pl. chl.}}{\text{Normal plasma chlorides}} \times 100$
2. Total salt content of the body $= 0.248$ per cent of body weight (gm.)

   From *1* and *2*:
3. Number of gm. of salt needed to restore body chlorides to normal
   $=$ per cent of body salt lost $\times$ total salt content of body
   $= \dfrac{\text{Normal pl. chl.} - \text{Actual pl. chl.}}{\text{Normal plasma chlorides}} \times 100 \times 0.248\%$ of body weight (gm.)
   $= \dfrac{560^{*} - \text{actual plasma chlorides}}{560} \times 0.00248 \times$ body weight (gm.)†

This formula becomes much simpler than it appears to be when applied to an actual case. For example, assume that one is dealing with a 60 kg. patient having plasma chlorides of 410 mg. per cent. The calculations under the conditions stated are as follows:

$$\text{Per cent of body salt lost} = \frac{560 - 410}{560} \times 100 = 26.8 \text{ per cent}$$

Total salt content of the body $= 0.248$ per cent $\times$ 60,000 gm. $= 148.8$ gm.
Gm. of salt needed to restore body chlorides to normal $= 26.8$ per cent of 148.8 gm. $= 39.9$ gm. Thus, this individual would need 39.9 gm. of salt, which, if given in the form of physiologic saline solution (0.85 gm. per 100 c.c.), would amount to 4,694 c.c.

*The normal plasma chloride concentration varies from 560 to 630 mg. sodium chloride per 100 c.c. The lower limit was selected for the calculations because many sick patients will not attain a higher level. If it is desired, a higher value may be used in the formula.

†In some laboratories whole blood chlorides rather than plasma chlorides are determined. Using 450 mg. sodium chloride per 100 c.c. as the normal for whole blood, the formula calculation would be:

$$\text{Gm. salt needed} = \frac{450 - \text{actual blood chlorides}}{450} \times 0.00248 \times \text{body weight (gm.)}$$

Experimental Observations.—In order to determine the practical value of these theoretical calculations, the formula was applied in the treatment of a series of cases with hypochloremia. Seven of the cases were the experimental subjects shown in Table VI in whom hypochloremia has been produced intentionally. These subjects were given salt in an amount approximately equal to that calculated to be necessary to restore the plasma chlorides to 560 mg. per cent. With one exception (G. W.), the salt was given intravenously in the form of physiologic saline or Ringer's solution at the rate of about 500 c.c. per hour. All of the urine was collected during the period of study and the salt excreted in this manner was determined. No other significant salt losses occurred.

The results of this study are shown in Table X. The close correlation between the amount of salt lost resulting in hypochloremia, the amount actually retained after salt replacement, and the calculated optimal retention based on the formula indicate that the theoretical principles of salt replacement that have been presented are sound. In two instances there is a noticeable discrepancy between the actual salt lost and the optimal retention calculated on the basis of the depleted plasma chloride level. In the case of G. W. the calculated optimal salt retention was considerably in excess of the actual salt lost. In this patient the unusually low plasma chloride concentration of 308 mg. per cent was produced in part by the forced ingestion of 3,400 c.c. of water by mouth in a short period of time. This resulted in the dilution of the chlorides remaining in the body. The use of this diluted plasma chloride concentration for the determination of the optimal salt retention resulted in a calculated salt need considerably in excess of the amount of salt which had actually been lost. In the case of H. A. about 16 gm. more salt were lost than were calculated to be necessary to restore the chlorides to normal. This discrepancy for the most part is accounted for by the unusually large excretion of salt in the urine (13.8 gm.) in the first two days on the salt-poor diet during which time no alteration occurred in the plasma chloride concentration.

The case of G. W. deserves additional comment for it illustrates a complicating factor in accurate salt administration. This patient was given 34 gm. of his total salt intake by gastric tube in the form of a 1.7 per cent solution. Soon afterward he passed two large watery incontinent stools estimated to be about 1,000 c.c. each. As pointed out by a number of workers, hypertonic salt solution stimulates peristalsis,[113-118] and thus its use may result in inaccuracies by provoking abnormal losses through diarrhea.

Eleven other patients shown in Table XI had low plasma chlorides when first they came to our attention. This group included instances of pyloric and intestinal obstruction, rectal polyp with profuse rectal discharge, paralytic ileus, and patients who had been on gastroduodenal

TABLE X

REPLACEMENT OF BODY CHLORIDES IN EXPERIMENTAL SUBJECTS WITH HYPOCHLOREMIA

(FORMULA CALCULATION BASED ON NORMAL PLASMA CHLORIDE LEVEL OF 560 MG. NaCl/100 C.C.)*

SUBJECT	BODY WEIGHT KG.	NACL LOST DURING PRELIMINARY AND DEPLETION PERIODS GM.	DEPLETED PLASMA CHLORIDES MG. %	PLASMA CO_2 COMBINING POWER VOL. %	NACL GIVEN GM.	NACL LOST			NACL RETAINED GM.	OPTIONAL RETENTION FORMULA CALCULATION GM.	FINAL PLASMA CHLORIDES MG. %	FINAL PLASMA CO_2 COMBINING POWER VOL. %	CLINICAL RULE GM.
						URINE GM.	STOOL GM.	TOTAL GM.					
R. W.	56.7	37.7	384	75.1	46.7	1.4	0	1.4	45.3	44.2	516	63.6	49.6
S. T.	73.2	35.2	436	67.3	42.8	0.5	0	0.5	42.3	40.1	554	56.3	45.4
G. W.	75.4	57.9	308	53.9	80.1	14.7	?	--	--	84.1	531	53.5	95.0
H. A.	76.9	52.3	454	49.5	38.2	0.7	0	0.7	37.5	36.1	545	60.7	40.8
J. W.	59.8	18.1	447	61.4	26.2	1.1	0	1.1	25.1	29.9	546	58.9	33.8
T. J.	72.7	36.3	427	59.9	40.6	0.0	0	0.0	40.6	42.7	564	48.0	48.3
W. P.	67.7	30.3	436	57.3	33.7	1.5	0	1.5	32.2	37.1	543	58.3	42.0

*Note the close correlation between the sodium chloride lost during depletion, the sodium chloride retained in restoring the plasma chlorides to normal, and the optimal retention. Note also the proximity of the final plasma chlorides to 560 mg. per cent.

TABLE XI

TREATMENT OF HYPOCHLOREMIA

(FORMULA CALCULATION BASED ON NORMAL PLASMA CHLORIDE LEVEL OF 560 MG. NaCl/100 C.C.)*

PATIENT	BODY WEIGHT KG.	INITIAL PLASMA CHLORIDES MG. %	INITIAL PLASMA CO_2—COMBINING POWER VOL. %	NaCl GIVEN GM.	NaCl LOST				NaCl RETAINED GM.	OPTIMAL RETENTION FORMULA CALCULATION GM.	FINAL PLASMA CHLORIDES MG. %	FINAL PLASMA CO_2 COMBINING POWER VOL. %	CLINICAL RULE GM.
					URINE GM.	GASTROINTESTINAL TRACT GM.	STOOL GM.	TOTAL GM.					
O. M.	63.3	404	57.6	55.8	7.7	7.3	0	15.0	40.8	43.7	559	52.0	49.6
B. S.	39.0	449	63.6	28.4	9.2	1.2	0	10.4	18.0	19.2	493	67.1	21.6
J. C.	65.5	479	45.7	27.5	2.6	1.4	0	4.0	23.5	23.4	586	44.7	26.5
D. C.	60.4	513	59.8	15.8	1.3	0	0	1.3	14.5	12.6	564	53.9	14.2
D. E.	58.1	345	100.0	100.6	6.2	38.1	0	44.3	56.3	55.3	606	73.0	62.5
L. A. D.	62.0	372	75.0	70.1	14.9	5.5	0	20.4	49.7	51.6	566	60.0	58.3
C. K.	48.9	356	48.0	56.8	0.7	1.1	17.9	19.7	37.1	44.1	528	49.8	49.8
S. L.	21.8	479	--	8.7	0.9	0	0.8	1.7	7.0	7.8	536	--	8.8
L. B. D.	54.0	464	--	25.7	5.4	0.3	0	5.7	20.0	22.9	554	--	25.9
B. M.	34.0	437	--	21.3	0.2	0	0	0.2	21.1	18.5	513	--	20.9
G. B.	45.3	352	--	61.5	10.9	4.8	0	15.7	45.8	41.7	510	--	47.1

*Note the close correlation between the sodium chloride retained and the optimal retention calculated on the basis of the formula. Also note the proximity of the final plasma chloride level to 560 mg. per cent.

suction without accurate replacement of the drainage losses with physiologic saline solution. These cases were treated in a manner similar to those already discussed, their chloride needs being calculated on the basis of their weight and their initial plasma chloride level. If the patient was losing chlorides through some abnormal source during the period of correction of the hypochloremia, these losses were replaced by the volume-for-volume rule. In a few cases small amounts of salt were given orally in addition to the intravenous administration. If the patient was dehydrated and the amount of fluid given as isotonic saline was not sufficient to correct the condition the extra water requirements were provided for by the intravenous administration of 5 per cent glucose in distilled water. In most of the patients a very satisfactory plasma chloride level was reached and there was a close correlation between the actual salt retained and the optimal retention as calculated by the formula.

Patient B. S. attained a plasma chloride concentration of only 493 mg. per cent. However, this seemed to be the maximum level for the patient at the time, for she excreted 9.2 gm. of salt in the urine and further administration of sodium chloride failed to raise the plasma chlorides significantly.

Patient C. K. was in a moribund state when she first came under our observation. She had a large rectal polyp associated with frequent watery stools and profuse rectal discharge. The salt content of this discharge was found to be 5.2 gm. per liter. Before half of the necessary salt had been administered, she was awake, and 24 hours after beginning the saline therapy she was sitting up in bed, mentally alert to the point of making witty remarks, and was taking food. One of the characteristic findings in these patients who are treated for hypochloremia is a definite euphoria as the plasma chlorides approach normal. The final plasma chloride level in this patient was only 528 mg. per cent but it will be noted that the actual salt retention fell 7 gm. short of the calculated need. This was due to the fact that the patient was losing more salt in the rectal discharge than we had anticipated, and so we had not made adequate allowance for this factor. The rectal polyp was removed and the patient left the hospital cured. If her moribund state had not been recognized as due to hypochloremia, she never would have come to operation.

The case of L. A. D. illustrates another instructive point. She was an 82-year-old female with a strangulated femoral hernia. Her calculated salt requirement was 51.6 gm. By mistake she was given 70.1 gm. Of the excess, 5.5 gm. were lost in gastroduodenal drainage and 14.9 gm. were promptly excreted in the urine, 49.7 gm. being retained. In general, we have found that small excesses of salt are readily eliminated by the kidneys, but, as has been pointed out previously, large excesses in sick patients tend to cause edema.

Patient G. B. is the case reported in detail in Table IV, illustrating the inability of some patients to attain a normal plasma chloride concentration.

In studying these patients we have found that some individuals will not attain the maximum plasma chloride concentration following the administration of a given amount of salt for a period of 36 hours. Falconer and Lyall[12] noted this same phenomenon and attributed it to chloride being stored in the tissues and later being used to raise the plasma chlorides. We have found that the individuals who are slow to reach a maximum plasma chloride concentration usually retain large amounts of water in the beginning, thus decreasing the salt concentration. As this excess water is excreted by the kidneys the plasma chloride level rises.

Clinical Rule.—As has been demonstrated, the formula for calculating the salt requirements of patients with hypochloremia is accurate, but for clinical purposes it is somewhat cumbersome, and a simpler rule was thought to be desirable. Accordingly, the following clinical rule based on the formula has been found to be very useful: *For each 100 mg. that the plasma chloride level needs to be raised to reach the normal, the patient should be given 0.5 gm. of salt per kilogram of body weight.* For example, if a 60 kg. individual has a plasma chloride level of 410 mg. per cent, the plasma chlorides need to be raised 150 mg. to reach the normal of 560 mg. per cent. The number of grams of sodium chloride required to accomplish this rise would be:

$$\frac{150 \text{ mg.}}{100 \text{ mg.}} \times 0.5 \text{ gm./kg.} \times 60 \text{ kg.} = 45.0 \text{ gm.}^*$$

It will be noted that this is only 5.1 gm. more than the figure obtained by the formula calculation for the same circumstances presented in an earlier paragraph. Because a patient receiving salt usually excretes a small amount in the urine, this slight excess is a desirable feature. The figures in the last column in Tables X and XI calculated on the basis of this clinical rule show a close correlation with the figures based on the formula calculation.

Complicating Factors.—Thus far the simple aspects of salt loss and replacement have been presented. There are, however, certain factors complicating the problem that are worthy of discussion. The chief of these is dehydration which almost invariably accompanies the abnormal loss of chlorides in clinical situations. Coller and Maddock[119] have dem-

*For those who are accustomed to expressing body weight in terms of pounds rather than kilograms, the following rule has been formulated: For each 100 mg. that the plasma chloride level needs to be raised, the patient should be given 0.2 gm. of sodium chloride per pound of body weight. This amounts to 39.6 gm. of salt for the example cited.

A clinical rule based on whole blood chlorides rather than plasma chlorides is as follows: For each 100 mg. that the whole blood chlorides need to be raised to reach the normal (450 to 500 mg. per cent), the patient should be given 0.6 gm. of sodium chloride per kilogram or 0.25 gm. per pound of body weight.

onstrated that a patient showing definite signs of dehydration has lost fluids amounting to about 6 per cent of his body weight. Thus, if a patient's dehydrated weight is used in calculating his salt requirements, less salt will be given than if his hydrated weight is used. Because hydration is the normal state, we believe that the patient's hydrated weight should be used in the calculations.* Dehydration also tends to concentrate the blood, which in turn raises the plasma chloride level. If the salt needs are calculated on the basis of this plasma chloride level, the amount of salt given again will be less than if the blood were not concentrated. It is possible to correct for this factor in the formula, but the excess of salt provided by the clinical rule of 0.5 gm. of salt per kg. of body weight for each 100 mg. rise in the plasma chlorides is sufficient to counterbalance the deficiency that might result in the calculations due to this concentration factor.

It has been mentioned previously that when sodium is lost abnormally from the body, water is also eliminated up to a certain point in an effort to keep the concentration of sodium in the body fluids constant. If sodium is lost in the same or greater amounts than chlorine (as indicated by a normal or low carbon dioxide-combining power), the chloride concentration of the plasma might be normal although significant amounts of both sodium and chlorine have been lost. Under such circumstances the plasma chloride level would not be of help in calculating the salt needs of the body. Such a patient, however, would be dehydrated as a result of losing body fluids containing salt, and so the suggestion of Coller and Maddock[119] of giving the patient fluids amounting to 6 per cent of his body weight in the form of physiologic saline solution should be followed.

Frequently the patient with a duodenal, biliary, or intestinal fistula or with a profusely draining wound presents a difficult problem in management. If all of the fistulous or wound drainage can be collected and accurately measured, the losses should be replaced by the volume-for-volume rule. Usually, however, the losses cannot be accurately measured. Two possible methods of management then remain. One is to determine the plasma chlorides at frequent intervals and give salt as indicated. This would insure keeping the body chlorides at a satisfactory concentration, but the laboratory work would prove time-consuming and expensive and it would not indicate whether or not too much salt was being given. The other method is to follow the daily salt content of the urine. As long as a patient excretes more than 1 gm. of salt per day in the urine, there is little danger of serious salt depletion. On the other hand, if large excesses of salt are given, this is usually shown by large amounts of salt in the urine. For these reasons, and

*If only the dehydrated weight is known, the hydrated weight can be calculated as follows:

Hydrated weight = Dehydrated weight ÷ 0.94

because determination of urinary chlorides is a simple procedure, this method seems to be the more practical of the two. As an added precaution the plasma chlorides should be checked every 7 to 10 days.

Still another difficult problem in management is illustrated by the case of F. F. (Table XII), a 21-year-old male, entering the hospital with nausea, vomiting, abdominal pain, and distention. The plasma chlorides were 462 mg. per cent. His calculated salt need was 25.5 gm. of sodium chloride. At operation a diffuse thickening and inflammation of the whole mesentery of the small intestine was found and about 1,400 c.c. of ascitic fluid were removed from the peritoneal cavity. During the first 24 hours, the patient was given 4,079 c.c. of physiologic saline solution containing 34.7 gm. of sodium chloride. During the same period, 14.6 gm. were lost in gastrointestinal drainage and ascitic fluid. The plasma chlorides rose only to 500 mg. per cent, but the patient gained 1.4 kg. in weight. During the next three days the gastrointestinal losses were replaced with equal volumes of physiologic saline solution and additional fluids were given in the form of 5 per cent glucose in distilled water. The plasma chlorides dropped progressively to 437 mg. per cent, and the ascites progressively became more marked. It was apparent that the patient was retaining water to develop ascites and in order to make the ascitic fluid isotonic, salt was being drawn from other parts of the body. When another large amount of salt was given, the plasma chlorides rose only to 515 mg. per cent and the ascites continued to increase. Throughout the entire period of study, the urinary output of salt remained less than 1 gm. per day. Porges[120] and Mach[121] also have noted the association of hypochloremia with ascites. The ideal method of managing such a case is not known, but this case does call attention to the fact that if a patient is developing ascites or hydrothorax, or edema, he will lower the concentration of the plasma chlorides unless considerable amounts of salt are provided. On the other hand, the administration of large amounts of salt will tend to increase the fluid retention. It is our opinion at the present time that, if the salt concentration of the body is decreased by the formation of ascites or hydrothorax, additional salt should be given to restore the chloride concentration to normal.

DISCUSSION

The term hypochloremia has been used frequently in this paper. Literally this term means a decrease in the concentration of the chlorides in the blood. This does not give a true conception of the condition which exists in these patients, because it implies that chlorides have been lost only from the blood; whereas, actually there has been a proportional loss from the interstitial fluids as well. We have used the term hypochloremia to mean a decrease in the total body salt as manifested by a

TABLE XII

CASE OF F. F. ILLUSTRATING THE DIFFICULTY IN MAINTAINING SALT BALANCE IN A PATIENT DEVELOPING ASCITES

24 HOURS ENDING 1938	BODY WEIGHT KG.	FLUID INTAKE					FLUID OUTPUT					NaCl LOSSES					
		ORAL C.C.	INTRAVENOUS 5% GLUCOSE IN DISTILLED WATER C.C.	INTRAVENOUS PHYSIOLOGIC SALINE C.C.	TOTAL C.C.	TOTAL NaCl INTAKE GM.	URINE C.C.	UPPER GASTROINTESTINAL TRACT C.C.	ASCITIC FLUID C.C.	STOOL C.C.	TOTAL C.C.	URINE GM.	UPPER GASTROINTESTINAL TRACT GM.	ASCITIC FLUID GM.	STOOL GM.	TOTAL GM.	PLASMA CHLORIDES MG. %
1-24	52.10	----	----	----	----	----	----	----	----	----	----	--	--	--	--	--	462
1-25	53.49	0	1,740	4,079	5,819	34.7	220	1,280	1,420*	0	2,920	0.1	7.5	7.1*	0	14.7	500
1-26	55.25	0	3,260	1,300	4,560	11.1	460	1,180	0	0	1,640	0.2	6.9	0	0	7.1	465
1-27	55.53	0	4,030	1,214	5,244	10.3	1,260	1,780	0	0	3,040	0.6	9.2	0	0	9.8	441
1-28	54.66	0	3,060	1,822	4,882	15.5	1,050	2,475	0	0	3,525	0.1	11.6	0	0	11.7	437
1-29	56.10	0	1,000	5,000	6,000	42.5	1,070	2,340	0	0	3,410	0.4	11.6	0	0	12.0	515
1-30	55.31	1,130	0	0	1,130	1.3	380	0	0	Incontinent	380	0.1	0	0	?	0.1	505
1-31	54.84	675	2,000	0	2,675	0.5	450	250	0	900	1,600	0.2	0.8	0	3.6	4.6	479
2-1	56.24	1,350	960	2,015	4,325	20.0	700	480	0	1,150	2,330	0.6	4.4	0	4.6*	9.6	515
Totals		3,155	16,050	15,430	34,635	135.9	5,590	9,785	1,420	2,050	18,845	2.3	52.0	7.1	8.2	69.6	

*Estimates.

decrease in the plasma chloride concentration. Perhaps a different term, such as "hypochloration," would more adequately convey the correct impression.

In referring frequently to chloride depletion and replacement, we have not wished to imply that the chloride ion alone is the one fundamentally involved. Undoubtedly the sodium ion is as important as, if not more important than, the chloride ion, but its determination is too complicated at present to be of use clinically. A fairly accurate estimate of the degree of depletion of the body sodium can be arrived at by a determination of the plasma carbon dioxide combining power in conjunction with the plasma chloride determination. However, from a therapeutic standpoint, in most clinical situations encountered by the surgeon correction of the chloride depletion with sodium chloride will also correct the sodium deficiency. Only in acidosis is sodium needed in excess of chloride. Even under such circumstances it is our belief that hypochloremia should first be corrected by giving the required amount of sodium chloride together with sufficient water and glucose to correct dehydration and ketosis. If, after the completion of such therapy, acidosis still persists, an attempt to correct it may be made by giving sodium lactate or bicarbonate. As mentioned previously, Gamble[107] has pointed out that if water and sodium chloride are abundantly supplied normal kidneys can be depended upon to correct the acid base balance of the plasma by excreting the ion not needed by the body. It has also been shown, especially by Haden and Orr,[65] that chlorides other than sodium chloride are unsatisfactory for the correction of hypochloremia.

Salt is always lost from the body together with water and to replace one without the other is physiologically unsound. It is apparent, therefore, that the salt needed for the restoration of body chlorides should be given in isotonic or hypotonic solution. Hypertonic solutions are faulty in that they further dehydrate the patient and, because of their stimulating action on the bowel, tend to produce inaccuracies in salt administration by causing losses in diarrheal stools. Furthermore, in reviewing Haden and Orr's experiments,[72] it is noted that a number of dogs with hypochloremia died during the administration of hypertonic salt solution. One of us (D. L. C. B.) has observed death in two cases of intestinal obstruction shortly after the administration of hypertonic salt solution. We have found that patients with hypochloremia will retain the salt needed if it is given intravenously at the rate of 400 to 500 c.c. per hour in the form of physiologic saline or Ringer's solution. If the patient is markedly dehydrated, additional fluids in the form of 5 per cent glucose in distilled water should be given to provide for water losses through the skin, lungs, and kidneys. This fluid may be added to or given alternately with the saline solution. When the

chlorides are very low, the total amount of fluid given may appear to be unusually large, but this, nevertheless, is the amount needed to restore the normal water and salt balance of the body.

A discussion of hypochloremia in relation to such nonsurgical conditions as diabetic acidosis, adrenal insufficiency, nephritis, and pneumonia has purposely been avoided because of the lengthiness of this paper and because these problems are usually not the immediate concern of the surgeon. However, the discussion of the subject of salt balance cannot be brought to a close without a few brief remarks concerning water intoxication.

Water intoxication, resulting from the excessive administration of water by mouth or rectum and characterized by headache, nausea, asthenia, muscular irritability, salivation, convulsions, and death, was first described in man in 1922 by Weir, Larson, and Rountree,[122] who correctly attributed it to an upset in the salt-water balance. They found that the condition could be corrected by the administration of salt solution and could be prevented if 10 per cent salt solution was given immediately before the administration of the water. Helwig, Schutz, and Curry[123] produced water intoxication in rabbits by proctoclysis of tap water. They found a marked fall in the blood chlorides and in the chloride content of the brain, kidney, and muscle. Autopsy of a fatal case of water intoxication in a human being reported by them showed a uniformly swollen brain with a rather dry outer surface, but the cut surface showed a smooth homogeneous "wet" appearance. Microscopically, there was an apparent increase in vacuolization of the stroma. In a later article Helwig, Schutz, and Kuhn[124] reported the recovery of a patient with water intoxication following the administration of hypertonic salt solution.

Cutting, Lands, and Larson[19] have showed that "the lethal value for infusions of 1 per cent solution of sodium chloride in cats is of the order of 500 c.c. per kilogram of body weight when the rate of injection is 5 c.c. per kilogram of body weight per minute. This would correspond in a man weighing 154 pounds (70 kg.) to 35 liters at a rate of 350 c.c. per minute." They found no evidence of cerebral edema in these animals receiving massive infusions of saline solution. The fatal case of water intoxication reported by Helwig and others[123] received only 9 L. of tap water by proctoclysis within a period of 30 hours. Thus, the administration of water must be quite different from saline solution in its physiologic effect on the organism.

Of fundamental importance in understanding the mechanism of water intoxication is the work of Darrow and Yannet[125] on the redistribution of water when electrolytes are lost without corresponding loss of water. They have pointed out that almost seven-tenths of the body is made up of water which moves between intracellular and extracellular spaces in such a manner as to maintain osmotic equilibrium between the fluid of

the cells and that of the extracellular spaces. Since about nine-tenths of the osmotic pressure of the body fluids is maintained by electrolytes, the distribution of body water is largely determined by the distribution of these electrolytes. The chief constituents within the cells are probably proteins, potassium, and phosphates. The chief constituents of the extracellular fluids are sodium and chloride. Osmotic equilibrium is maintained largely by a shift of water from one side of the cellular membrane to the other. If the amount of electrolyte in the extracellular fluid is decreased, water passes into the cells from the extracellular spaces in order to equalize the electrolyte concentration on both sides of the cell membrane. Thus, the cells swell due to their increased water content.

From this we see that if a large amount of water is given rapidly to an individual with a normal salt concentration in the extracellular spaces, this concentration will be somewhat decreased due to dilution; water will pass into the cells to establish osmotic equilibrium; and mild symptoms of water intoxication will result. However, if the patient has been depleted of electrolytes, the salt concentration in the extracellular spaces is already at a critically low level. If the concentration of the electrolytes is suddenly decreased further by the administration of large amounts of water, the cells will swell markedly and severe symptoms of water intoxication will result. Swelling of the cerebral tissues causes the convulsions which characterize the end stage of this condition. Thus, the grave danger of giving water to a patient with hypochloremia and therefore with depleted electrolytes is apparent.

The treatment of water intoxication consists in the prompt administration of sodium chloride, and in this instance hypertonic saline given intravenously is the solution of choice.

Many problems of salt balance in surgical patients are still unsolved. Further studies are in progress at the present time in an effort to clarify some of them.

SUMMARY AND CONCLUSIONS

The maintenance of a proper salt balance is an important clinical problem commonly encountered by the surgeon. Practical aspects of salt metabolism in surgical patients have been presented, it being emphasized that excessive salt administration is apt to lead to the development of edema; whereas, loss of salt by vomiting, gastroduodenal suction, duodenal, biliary, and intestinal fistulas, diarrhea, wound drainage, or profuse sweating will lead to serious disturbance of the body chemistry. Loss of body chlorides, characterized by hypochloremia, is manifested clinically chiefly by lassitude, weakness, drowsiness, coma, anorexia, nausea, low pulse pressure, and dehydration.

It has been found that hypochloremia can be prevented if all abnormal fluid losses from the body are replaced with equal volumes of physiologic

saline solution. It has also been found advantageous to give 1 L. of physiologic saline solution during the first 24 hours of abnormal fluid loss in addition to the volume-for-volume replacement. This rule has been found especially useful in the management of patients with indwelling gastroduodenal suction.

For the accurate replacement of salt in patients whose body chlorides have been depleted, a simple formula has been developed based upon body weight and plasma chloride concentration. From this formula a clinical rule has been derived for the management of patients with hypochloremia; namely: for each 100 mg. per cent that the plasma chlorides need to be raised to reach the normal, the patient should be given 0.5 gm. of salt per kilogram of body weight in the form of physiologic saline or Ringer's solution. This rule has been found to work well in practice.

A number of complicating factors have been presented, and the relationship of hypochloremia to water intoxication has been discussed.

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Review of Recent Meetings

THE AMERICAN PROCTOLOGIC SOCIETY

CURTICE ROSSER, M.D., DALLAS, TEX.

(From the Section on Proctology, Baylor University Medical School)

THE thirty-ninth annual meeting of the American Proctologic Society was held June 11, 12, and 13, 1938, at the St. Francis Hotel in San Francisco, Calif. This group has a fellowship limited to seventy-five with one hundred associate members.

In his presidential address, **H. Z. Hibshman,** Philadelphia, Pa., stressed the present need for additional graduate teaching of proctology and the necessity for continued efforts to set up proper standards for the specialty with a mechanism for certification of proctologists. He further suggested the possible advisability of a national journal for the specialty.

The history of proctology and the management of prolapse of the rectum were featured on the scientific program. **A. J. Zobel,** San Francisco, Calif., related incidents in connection with the development of the Society during the past three decades; **G. S. Hanes,** Louisville, Ky., delivered the biennial Joseph Matthews Address, recapitulating the history of the specialty from the period of his former associate, the world's first proctologist, Dr. Matthews. As part of the same symposium, **M. R. Hill,** Los Angeles, Calif., presented excellent photographic reproductions demonstrating the development of the art of illustration in connection with rectal diseases. In the **Symposium on Prolapse, R. C. Alley,** Lexington, Ky., reported an application of the Reid compression ligature for use in correcting prolapse of colostomy stoma; **M. L. Emerson,** Oakland, Calif., criticized the use of the elastic ligature for extensive prolapse of the rectum because of unfavorable results in his hands due to part of the colon's being caught by the constricting ligature; **A. J. Murrieta,** Los Angeles, Calif., described a new technique for correcting rectal prolapse, which is in effect a modification of his own valvotomy operation as reported in the 1931 Transactions of the American Proctologic Society. This procedure is carried out under a low spinal anesthesia and consists in wide excision of several segments of the rectal mucosa at different levels in a horizontal direction. **Dudley Smith,** San Francisco, Calif., reported favorable results in prolapse in twelve cases treated by several massive injections of 1:1,500 hydrochloric acid under anesthesia; **H. T. Hayes,** Houston, Tex., advocated castor oil with 1 per cent phenol used in a similar manner and **E. H. Terrell,** Richmond, Va., suggested the submucosal injection of 3 per cent quinine urea hydrochloride for mild prolapse.

Rare tumor formations about the rectum and anus were reported by **W. R. Rainey,** St. Louis, Mo.; **R. L. Murdoch,** Oklahoma City, Okla.; **S. B. Kleiner,** New Haven, Conn.; and **J. F. Saphir,** New York, N. Y. **F. B. Campbell,** Kansas City, Mo., reported an interesting case of a patient with multiple foreign bodies, and **W. P. Black,** Charleston, W. Va., and **C. E. Pope,** Evanston, Ill., demon-

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strated new instruments for diagnostic and therapeutic purposes. Pope's instrument permits routine proctosigmoidoscopy, fulguration, electrocoagulation, or spray medication under a closed system. The electrode or spray is attached to a sliding sleeve. A suction tube with a release valve actuated by air infiltration removes smoke, or regulates light constant pressure, thereby obtaining precision, rapidity, and ease of operation. **M. S. Kleckner,** Allentown, Pa., discussed the importance of low spinal anesthesia in proctologic operations, believing it a satisfactory anesthetic for either anal or colonic surgical procedures. He prefers spinocain and varies the dose from 40 to 200 mg., and, with the exception of postoperative headache in a small percentage, has experienced no complications. **M. S. Woolf,** San Francisco, Calif., discussed the curability of chronic ulcerative colitis, basing his remarks on an analysis of seventy records of cases from the University of California Hospital. Woolf feels that, in spite of the unsatisfactory results of medical treatment, including the high percentage of recurrence and the absence of a specific curative therapy, the results and dangers of surgery, especially ileostomy and colectomy, make operative procedures even less desirable and concludes that the treatment of chronic ulcerative colitis should be purely medical. **N. D. Smith,** Rochester, Minn., agreed that medical measures had been more satisfactory in his hands than surgical procedure with the exception of complete colectomy, and **A. B. Wilcox,** Santa Barbara, Calif., felt that some of the unfavorable results in surgery in this disease resulted from a tendency to subject only moribund cases to operative procedures. **M. C. Pruitt,** Atlanta, Ga., from a study of 206 answers to questionnaires sent to proctologists and general surgeons found a remarkable variation in methods of treatment used for various minor anal lesions. The majority made a distinction in the treatment of early fissures and subsequent ulcers. Eighty-three injected anesthetics for fissure and the majority favored excision when ulcer is present. About one-half favored two-stage operations for complex fistulas; local applications were favored for mild pruritis, but forty-four methods were suggested for severe pruritis. The fungi are not regarded as etiologic by most of those questioned. Electrical methods have apparently been largely discarded for the treatment of internal hemorrhoids; injection is favored for early hemorrhoids; excision and suture is the most popular operative procedure. There was an almost equal division concerning early or late removal of strangulated hemorrhoids. The majority of those who answered the questionnaire kept patients in the hospital for an average of six days after hemorrhoidectomy. **A. W. M. Marino,** Brooklyn, N. Y., and his associates **A. M. Buda** and **I. Skir** presented a comprehensive review of the problem of anal tuberculosis. They believe that approximately 5 per cent of all individuals with tuberculosis develop fistula and report that 11 per cent of 367 fistulas seen by them proved to be tuberculous. Guinea pig inoculation with sectioning of the animal's enlarged nodes is the ideal diagnostic method. While Marino originally used the cautery in fistulectomy, he now uses sharp dissection without untoward effects. **A. J. Chisholm,** Denver, Colo., stated that the majority of tuberculous fistulas occur in institutional patients where concentrated food and inactivity cause constipation, with resultant fissure or cryptitis. The anal abrasions are subsequently invaded by swallowed acid-fast organisms in the stool. Chisholm found tubercle bacilli in 77 per cent of cases with active phthisis and in 55 per cent of cases with arrested pulmonary lesions. They were not found in 106 cases free from pulmonary tuberculosis. His surgery is done with a modified Percy cautery, which he believes more effective and less dangerous than the scalpel. He has found that activity of the disease in the chest is no bar to surgical procedures.

The very extensive literature on various phases of anorectal and colonic disease, which appeared in 1937, was reviewed in detail by **H. I. Silvers,** Atlantic

City, N. Y. **H. I. Kallet,** Detroit, Mich., opened the discussion on the subject of radiation in the treatment of pruritis ani; the conclusions of **W. W. Green,** Toledo, Ohio; **V. G. Jeurink,** Denver, Colo.; and **D. C. McKenney,** Buffalo, N. Y., were that this form of treatment is often helpful temporarily and occasionally effective permanently. It is important that the dosage be kept within non-injurious limits. **T. E. Smith,** Dallas, Tex., reported a specific diagnostic scratch test for chancroidal ulceration and reviewed the results of the treatment of this lesion with progressively increased intravenous injections of 1 per cent mercurochrome as originally suggested by **Curtice Rosser,** Dallas, Tex. This specific therapy has been employed for ten years in the dispensaries of the Medical Department of Baylor University.

N. D. Smith, Rochester, Minn., reported a series of cases in which perianal pyodermia simulated extensive anal fistula. Where this condition becomes chronic, Smith believes a radical excision is necessary. **H. E. Bacon,** Philadelphia, Pa., reported a large group of multiple malignancies of the lower bowel, some of which were apparently primary and others due to contact. In the discussion of his paper, **T. E. Jones,** Cleveland, Ohio, stated that, while he himself had seen 6 instances (5 of them involved the sigmoid and rectum and the other the cecum and the rectum), the incidence is so low (about 1 in 250 cases) that he did not believe it justified insistence upon protracted x-ray examination in every case where a single malignancy is discovered. **Howard A. Brown,** San Francisco, Calif., discussed the relief of intractable pain due to inoperable rectal cancer. In the experience of **H. C. Naffziger,** San Francisco, Calif., and himself, intradural injections of alcohol have not proved satisfactory and sections of the sympathetic nerves alone have been even less helpful. They, therefore, advocate chordotomy. **Dudley Smith,** San Francisco, Calif., felt that alcohol injections had given relief to so many patients in his hands and those of others and that the procedure is so much less hazardous than chordotomy that he believed the therapy originally suggested by Dogliotti should be given further trial. **T. E. Jones,** Cleveland, Ohio, stated that, even in unoperable malignancy of the rectum, excision of the primary growth is often justifiable for the relief of pain and that liver metastasis is not a bar to this step.

At the conclusion of the 1938 session, an invitation from the British Sub-Section on Proctology to conduct a joint meeting of the two organizations in London in June, 1939, immediately following the regular annual meeting of the Society in this country, was accepted and **Dudley Smith,** San Francisco, Calif., was elected President of the organization for 1938 to 1939.

The complete transactions of this meeting are available in book form under the editorship of **H. E. Bacon,** Philadelphia, Pa.

REPORT OF THE SECTION ON GENERAL AND ABDOMINAL SURGERY OF THE MEETING OF THE AMERICAN MEDICAL ASSOCIATION, SAN FRANCISCO, CALIF., JUNE 13–17, 1938

LEON GOLDMAN, M.D., SAN FRANCISCO, CALIF.

(From the Department of Surgery, University of California Medical School)

WALTMAN WALTERS, Rochester, Minn.: **Surgical Lesions of the Adrenal Gland.**—The clinical aspects of seven cases of adrenal cortical tumor were presented. These patients had their tumors removed without a death, and the symptoms were alleviated in all.

Adrenal cortical adenomas must be differentiated from the basophilic adenoma of the pituitary gland and the arrhenoblastoma of the ovary. Some of the differential points were discussed by the speaker. Masculinization of the female, characterized by hirsutism, acne, obesity, hypertrophied clitoris, and change in voice rather uniformly appeared in the patients with adrenal cortical adenoma. In the surgery of adrenal cortical tumors the preoperative and postoperative care is particularly important, as these patients may die of adrenal cortical insufficiency, unless this hormone is supplied in large amounts. Sodium chloride and sodium citrate solutions should be administered both before and after operation. The paraganglioneuromas are the common tumors of the adrenal medulla and are characterized by paroxysmal hypertension, in contradistinction to the sexual changes produced by the cortical tumors.

Dr. Walters has discontinued the use of perirenal injections of air as a roentgenologic diagnostic procedure, because the tumor is often so small that its outline is not perceptible and also because of the danger of fatal air embolism.

Howard C. Naffziger, San Francisco, Calif., stressed the importance of proper preoperative and postoperative management in these cases. He stated that in so-called "basophilism" of the pituitary gland there may be either hyperplasia or adenoma of the adrenal cortex. He was inclined to feel that there may be two distinct clinical pictures, either the adrenal genital syndrome with reversal of sex, associated with adrenal cortical tumors; or the Cushing syndrome, in which there may be altered cortical function as evidenced by overproduction of cortin.

Hans Lisser, San Francisco, Calif., stated that the differential diagnosis of the three foregoing conditions is often very difficult. The distinction between arrhenoblastoma and adrenal cortical tumor is difficult because these two conditions often cause identical changes. He felt that the hormone test might be of value in the recognition of adrenal hyperplasia, and, because of the great difficulty of diagnosis, advocated the use of air injection to obtain roentgenological evidence of tumor.

Virgil Harlan Moon, Philadelphia, Pa.: **Early Recognition of Shock and Its Differentiation From Hemorrhage** (paper read by **J. P. Schaeffer,** Philadelphia, Pa.).—The author stressed the point that shock should be recognized and treated during its earliest stages and that, after the blood pressure descends below the

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critical level of 80 mm., the patient's condition is serious. Blood volume and flow should be the chief criteria for shock rather than the presence of a lowered blood pressure. The author found by experimental and clinical observation that the hemoconcentration is proportional to the gravity of the condition and that this concentration occurs early, often before the blood pressure begins to drop. The hemoglobin and red blood cell count, especially the latter, are dependable guides to the concentration of the blood. A 20 per cent concentration of the blood may take place without other evidence of shock. When a 40 per cent concentration of the blood is reached, the patient's condition is grave.

In hemorrhage there is hemodilution rather than hemoconcentration and this dilution is proportionate to the amount of blood lost.

Hemoconcentration is the result of the shock mechanism and is the earliest clinical test we have to detect it. The author made a plea for serial red blood counts in cases in which shock might be suspected.

J. Eastman Sheehan, New York, N. Y.: **The Use of Free Full Thickness Skin Graft.**—In the author's hands free, full thickness skin grafts have been efficacious in more than 95 per cent of applications. The advantages of this method are that it produces no surface defects and there is no change in pigmentation. The patients must be in good general health. Important factors in the process of such a procedure are the preparation and state of the skin and grafted area, atraumatic technique, use of pressure dressings with immobilization, and the administration of vitamin B if necessary. If, following surgery, the temperature becomes elevated or there is a discharge or odor, the presence of infection must be assumed, and the use of certain remedial measures oftentimes insures the survival of the graft. A beautiful colored motion picture was shown depicting the method of transplanting the graft.

George W. Pierce, San Francisco, Calif., stressed the importance of hemostasis, inasmuch as hemorrhage into the graft might cause its loss. He also stated that pigmentation is likely to occur in 20 per cent of the cases and probably will be marked in from 8 to 10 per cent.

H. F. Kirkham, Houston, Tex., stated that full thickness grafts could not be transplanted to the face of a negro because of the marked increase in pigmentation.

Charles Scott Venable, San Antonio, Tex.: **Electrolysis: The Controlling Factors in the Use of Metals in Fractures.**—Dr. Venable presented evidence gained by clinical means and animal experimentation to show that metal used for internal fixations of fractures will corrode if electrolysis develops. He demonstrated that, the body fluids being the electrolyte, electrolytic action takes place between metals and bone, by the transposition of ions, in accordance with the law of the electromotive force of metal. Without electrolysis, there can be no corrosion of metal. An alloy of cobalt, chromium, and molybdenum called vitallium has been shown through all experiments to be noncorrosive and so electrically neutral that it causes no tissue or osseous change. In addition its tensile strength compares favorably to that of other metals used. Dr. Venable showed several lantern slides of roentgenograms of patients for whom screws, plates, and nails prepared of vitallium had been used without evidence of corrosion of the metal or resorption of bone around them. Osteogenesis is not interfered with. The author proposed vitallium as the ideal metal for internal fixation because of its lack of electrolytic properties and its potential strength.

Leon Parker, San Francisco, Calif., remarked that the steel alloy metals are not permanently tolerated and that vitallium should answer the purposes of the orthopedist.

Martin B. Tinker, Jr., Ithaca, N. Y.: **Fracture of the Neck of the Femur.**—The speaker reviewed statistics on methods of external fixation for fractures of the neck of the femur and emphasized the high mortality, high incidence of nonunion, deformity, ankylosis, muscular atrophy, and prolonged hospitalization. The advantages of internal fixation of the neck of the femur are that the method usually is not associated with shock; the patient is immediately relieved of pain and may be up sooner. In competent hands most of the disadvantages mentioned above can be avoided by the use of internal fixation. This fixation should be firm enough to insure union, with considerable freedom of bodily movement. It was his opinion that, by the use of three Moore nails, better holding could be secured than by the use of one Smith-Petersen nail.

Kellog Speed, Chicago, Ill., stated that with immediate reduction of the fracture there are relief from pain and restoration of the patient's confidence. Because, in many cases, there is a tendency for the nail to lose the position of the fracture, he does not permit weight-bearing for from sixteen to twenty-four weeks.

E. W. Cleary, San Francisco, Calif., demonstrated by the use of lantern slides a special table which he devised. This table has instruments attached to act as a guide for the insertion of the nail. He claimed that some of the dangers of internal fixation were obviated by the use of this particular equipment.

Walter G. Stern, Cleveland, Ohio, felt that the introduction of a nail is a major operation which carries an operative mortality of 26 per cent. He advocated a subtrochanteric osteotomy for ununited fractures in order to convert the shearing force to a compression force which would then permit union to take place.

George W. Swift, Seattle, Wash.: **Cerebrocranial Injuries: Detailed Study of 1,433 Cases.**—Dr. Swift made a study of 1,433 cases of cerebrocranial injuries, treated in approved hospitals in the state of Washington over a period of one year. By familiarizing the staffs of the different hospitals with a definite program of treatment for head injuries, he felt that the mortality had been lowered. He advocated treatment of early shock and observation of the patient for hemorrhage, and stressed the control of water balance by means of spinal puncture, which he considered a very important factor in lowering the mortality. The control of secondary shock was mentioned. Massive hemorrhage cannot be controlled, but meningeal hemorrhage can be. Seventy-five and seven-tenths per cent of the patients who left the hospital, did so in one week. There was a mortality of 15 per cent for the series.

Harry E. Mock, Chicago, Ill., used cases of proved fracture of the skull as a measuring rod for his series. There are about 500,000 head injuries in the United States yearly. He divided his cases into two groups: fractures of the skull and fractures of the skull with blood in the spinal fluid. In the large series studied, from 50 to 60 per cent of the patients in the latter group died within twenty-four hours. He did not advocate routine measures in all cases and emphasized the need of early neurosurgical consultations. He utilized dehydration treatment in a series of 275 cases, carrying out spinal puncture in 34 per cent of patients with proved

skull fractures and 90 per cent of those with blood in the spinal fluid. In his opinion subarachnoid hemorrhage is an indication for spinal puncture. In over 80 per cent of the cases spinal puncture was done within twenty-four hours, approximately 20 c.c. of fluid being removed, with a mortality of 17.7 per cent. He thought it would be necessary to do a cranial operation in from 8 to 10 per cent of fractures of the skull, either for a depressed simple or compound fracture, an extradural hemorrhage, or a subdural collection of blood or fluid. Associated injuries are important and should not be overlooked.

Arthur Carroll Scott, Temple, Tex.: **The Early Differential Diagnosis of Breast Tumors.**—Dr. Scott devised a new method of physical examination to detect early carcinoma of the breast by eliciting the so-called "cancer shadow." This test is made possible because of the early invasion of cancer along the interlobular fascia and Cooper's ligament which attaches to the skin so that it drags on the skin and subcutaneous tissues. By using tangential illumination with a spotlight, in a dark room, and by supporting the breast properly, a depression shadow over the cancer area is seen. In his experience this cancer shadow was found to be accurate in 94 per cent of the malignant cases, and in 88.9 per cent of the benign cases, with a total accuracy of 91.6 per cent. He felt that by the use of this test one would often be able to avoid biopsies which run a risk of spreading the cancer during the surgical removal of the breast.

Irving Abell, Louisville, Ky., stated that he felt the cancer shadow test to be tenable only when the cancer is superficial enough to involve this superficial layer of Cooper's fascia. If the cancer were deep in the breast, the test might be negative. He also said that every tumor of the breast should be removed, whether benign or malignant, and when doing a biopsy for carcinoma, the entire tumor should be removed as the biopsy specimen, rather than cutting into the cancer and excising a small piece of tumor tissue.

Hugh H. Trout, Roanoke, Va., gave the **Chairman's Address** in the form of a demonstration, by colored motion picture, of a radical mastectomy conforming to the method devised by Halsted. Dr. Trout emphasized the importance of using the electric knife for taking biopsies of the breast and of removing the entire tumor when so doing. He stressed the main features of the operation as removing a wide margin of skin, depending on skin graft in cases of large tumors, and complete removal of the pectoral muscles and axillary lymph nodes. Radiation therapy should not supplant surgery but should be used in addition to it. Dr. Trout advocated implants of radium, especially over the region of the internal mammary vessels, at the end of the operative procedure. In addition, preoperative and postoperative radiation should be used. He utilized silk technique throughout. In the cases in which there was a large single metastatic lymph node in the axilla, the prognosis was much better than if multiple smaller lymph nodes were involved.

Howard M. Clute, Boston, Mass.: **Gastroduodenostomy for Certain Duodenal Ulcers.**—The speaker thought that in certain cases of duodenal ulcer an anastomosis could be made between the stomach and the second portion of the duodenum, with alleviation of symptoms. This procedure is facilitated by complete mobilization of the second portion of the duodenum after incising the lateral parietal peritoneum along the duodenal margin. The great advantages of this operation are that it does not cause shock, it carries a lower mortality than gastric resection, and it is followed by a very small incidence of stomal ulcers, only three having been reported in over 400 cases collected from the literature. It is satisfactory for

use in the relief of pyloric stenosis, and, in the treatment of a bleeding duodenal ulcer, it may permit exposure and suture of the ulcer as well as obviating the sequela of a gastrojejunostomy. In the treatment of a bleeding gastrojejunal ulcer, gastroduodenostomy may be resorted to in those patients who are poor risks, after the gastrojejunal stoma has been taken down. If the patient is a good risk, a gastric resection should be done; otherwise it is best to take down the stoma and do a gastroduodenostomy. In cases of a high gastric ulcer it may be wiser merely to excise the ulcer and do a gastroduodenostomy rather than to attempt a high gastric resection which may be associated with a greater operative mortality. In the patients operated upon, however, there is a high gastric acidity following surgery, but the incidence of stomal ulcers is nevertheless very low, which obviates this complication of gastroenterostomy.

Robert S. Dinsmore, Cleveland, Ohio, thought this an excellent procedure, especially after taking down a gastrojejunocolic fistula. He prefers gastroduodenostomy to doing a resection of the stomach when so much surgery is necessary.

Harold Thompson, Los Angeles, Calif., noted experimentally that the more of the stomach one removed, the lower the subsequent gastric acidity became, and that the procedure described by Dr. Clute does not cause this change.

John Oscar Bower, Philadelphia, Pa.: **Routine Operations Versus Scientific Management of Spreading Peritonitis Complicating Acute Perforated Appendicitis.**—Dr. Bower emphasized the fact that recovery from acute infections of the peritoneal cavity depends on the development of immunity in general and local tissues, much as in the recovery from any other acute infection. Seventy-one per cent of the patients who recovered from spreading peritonitis showed an antitoxin for *Clostridium welchii* toxin in the blood serum. Patients do not die of appendicitis or of local peritonitis, but rather of spreading peritonitis. In the group of patients reported, the mortality of spreading peritonitis was 26.9 per cent, but it rose to 37.4 per cent in the patients who were operated upon. Dr. Bower showed definitely that there is a higher mortality if the patient is operated upon during the fifth or sixth day of the disease than at any other stage of the inflammatory process. In the attempts of localization of peritonitis about a perforated appendix, he stressed the importance of the peripheral zone of inflammation about the central point, where attempts are made to create a barrier. Operation frequently breaks down this barrier, allowing the spread of peritonitis. Ten per cent of the deaths that occur in spreading peritonitis follow the drainage of appendiceal abscess; consequently the speaker made a plea for extraperitoneal drainage in these cases, even though a second incision may be required to enter the abscess directly. Thirty-three per cent of the patients showed an antitoxic titer to the Welch bacillus in the peritoneal exudate. Dr. Bower advocated the Ochsnerization of spreading peritonitis until localization had taken place, and the use of perfringens bacillus antitoxin. Patients get their first dose of antigen during the attack of appendicitis, the second when the appendix ruptures; then, after localization takes place, if operation on the patient with ruptured appendicitis is routine, the surgeon often gives the patient the third (so often the fatal) dose of antigen by breaking down the barrier. Among 365 surgeons who operated on 18,000 patients, the incidence of spreading peritonitis was 27 per cent. Dr. Bower emphasized the fact that children should be treated in the same manner as adults and that they develop immunity as adults do. He advocated the use of drains for perforated appendicitis of all types and advised that the drains be left in place for seven days.

Charles G. Johnson, Detroit, Mich.: **The Use of Small Intestine Decompression and the Treatment of Intestinal Obstruction.**—The author has utilized the method of intubation of the small bowel up to the point of the obstruction with continuous suction in order to remove the fluid, as in an enterostomy, thereby overcoming abdominal distention. Obstructions caused by strangulation are not to be included in this type of treatment. The tube, which is passed through the nose, consists of a No. 18 soft rubber nasal tube, about ten feet long, to which is attached a tube of small caliber, with an inflatable balloon at the end. The balloon is inflated after the tube is in the duodenum and from that point the tube is carried down to the point of the obstruction by peristalsis. This method is used to facilitate operative procedures in the treatment of simple intestinal obstruction and is not a substitute for surgery. It has the advantage that it tides the patient over the danger period so that an operation can be carried out, it completely controls the distention, and it may aid in localizing the obstruction by passing the tube down to the point of obstruction and allowing a small amount of barium to go through. In obstruction low in the small bowel the patient's nutrition may improve by having the tube at the site of obstruction and allowing the absorption of food, preferably taken by mouth; fluids also may be given through the tube if desired. It is an excellent method for the treatment of paralytic ileus. Suction from a tube in the stomach or duodenum will remove only that fluid and gas brought to the level of the tube, and only secondarily releases the tension of the dilated loops just proximal to the obstruction; this tube, however, has the effect of an enterostomy without the operative dangers. The method is excellent for preparing the patient for operation, in that it overcomes the dangers which normally are present in the handling of dilated bowel.

Frederick Coller, Ann Arbor, Mich., stated that decompression, as advocated by Wangensteen, was the greatest contribution to abdominal surgery during the last decade. The associated abnormal chemistry is important and may cause death if a marked hypochloremia is present. If the patient's blood chemistry is normal at the start, the administration of normal saline solution will replace the loss of fluid, volume for volume. In case the blood chloride is lowered, allowing 0.5 gm. of salt for each 100 mg. that the blood chloride is lowered, and multiplying by the patient's weight in kilograms, will give an idea of how much chlorides should be administered.

Fred W. Rankin, Lexington, Ky.: **One Stage Combined Abdominoperineal Resection of the Rectum for Cancer.**—Dr. Rankin reported seventy-five cases of abdominoperineal one-stage resection of the rectum with a mortality of 6.6 per cent and an operability of 76 per cent. He stressed the importance of fitting the procedure to the patient and not the patient to the procedure. The spread of rectal cancer along the superior hemorrhoidal vessels into the mesentery of the sigmoid, and less frequently laterally, demands wide removal of bowel and contiguous tissue. This type of operation can be satisfactorily carried out only by sacrificing the sphincter mechanism and accepting a colostomy. The Miles operation is the only one which permits complete removal of the zone of spread of the cancer. In specimens removed by this procedure, the incidence of metastatic carcinoma found in the lymph nodes removed with the specimens varied from 50 to 70 per cent of the cases. Patients with cancer of the rectum require a long period of preoperative care so that the general condition may be built up and the bowel thoroughly cleansed. Occasionally, because of the patient's condition or other factors, a Lockhart-Mummery type of operation is done. Dr. Rankin emphasized that the colostomy loop should be rather taut and without slack, to prevent prolapse later. He also stressed peritonization of the operative area to prevent subsequent obstruction. He showed lantern slides demonstrating the technique of the operation.

Thomas M. Joyce, Portland, Ore., stressed the importance of suturing the mesentery of the sigmoid colon to the lateral parietal peritoneum to prevent a loop of small bowel slipping through and causing obstruction, when the colostomy loop is brought out through a stab wound. He also emphasized the importance of making a large enough stab wound when bringing the colostomy loop out. In his experience the operability rate at a charity hospital was only 23 per cent, while that at a private hospital was 60 per cent.

Albert O. Singleton, Galveston, Tex.: **The Problem of Disruption of Abdominal Wounds and Postoperative Hernia.**—The commonly accepted causes of disruptions of abdominal wounds are infection; hematomas; delayed wound healing; undue strain by vomiting, coughing, or distention; faulty suture material, allergic reaction; and hypoproteinemia. The author added nonanatomic incisions as an important cause. The muscles in the upper abdomen are respiratory muscles and therefore an incision so placed undergoes more strain than one in the lower abdomen. The author made a plea for not incising muscle fibers transversely. In the usual rectus and midline incisions the transversalis muscle and posterior rectus sheath are usually incised longitudinally, thereby cutting through their fibers, which is nonanatomic. The author suggested the use of the Sloan incision. This is made longitudinally through the skin and the anterior rectus sheath but the recti muscles are retracted so as to allow the transversalis muscles and posterior sheath to be opened transversely in order not to sever their fibers. The lateral transverse incision is a paracostal one, made in the line of the muscle fibers, and is utilized for cholecystectomy when placed on the right side, or splenectomy on the left. It is made in the same manner as a McBurney incision by splitting each layer parallel with the course of its fibers. In a controlled series of cases the author noted an incidence of disruption in 1.02 per cent and hernia in 2.24 per cent of the so-called nonanatomic incisions, such as rectus or midline. With the use of the anatomic incision, the incidence of disruption was only 0.0031 per cent and of hernia 0.92 per cent. Other types of well-known anatomic incisions are the Pfannenstiel and the McBurney. The author feels that if incisions are made anatomically without severing muscle fibers, the incidence of hernia and disruption can be reduced.

R. L. Sanders, Memphis, Tenn., stated that the mortality of wound disruptions is from 25 to 40 per cent and that, in 500 of his own cases of cholecystectomy, the incidence of postoperative hernia was 8 per cent. He attempted, therefore, to use a more anatomic incision than he had used previously. He now utilizes a transverse incision across the epigastrium, going through the anterior rectus sheaths transversely, dissecting these sheaths upward off the underlying recti muscles, then retracting the recti muscles laterally and opening the transversalis muscle and peritoneum transversely, thereby not severing any muscle fibers. He made the point that because disruption never occurs after a McBurney incision, he utilizes the McBurney principle in the upper abdomen. Preservation of motor nerves is also an important factor.

Alton Ochsner, New Orleans, La., stated that the lateral transverse incision might be utilized, although he has had no experience with it. He remarked that in delayed healing he considers it of great importance to use silk sutures even though working on an infected case. If infection is anticipated, it is more urgent to use silk sutures rather than catgut in order to maintain the strength of the wound. He recommended that the silk be fine and interrupted and stated that many times infection would be avoided in an otherwise potentially infected wound.

Hugh H. Trout, Roanoke, Va., stated that there is a wide variation in the strength of catgut which varies with the age of the animal from which it was prepared. He urged the proper preparation of debilitated patients for surgery as a precaution against disruption of wounds and postoperative hernia.

Frank G. Boland, Atlanta, Ga., is opposed to through-and-through sutures of the abdominal wall because of the danger of trauma to the bowel and peritonitis. He stressed the importance of firm closure as well as the necessity for exact closure of the peritoneum and the transversalis muscle.

Charles E. Phillips, Los Angeles, Calif.: **Mediastinal Infections Due to Esophageal Perforations.**—Dr. Phillips stated that it is the conception of medical authorities that acute suppurative mediastinitis is always fatal, particularly if it is due to a perforation of the esophagus. The esophagus is a very frail structure and injury by esophagoscopy or foreign bodies is not infrequent. Perforation usually occurs in the upper part of the esophagus due to contraction of the pharyngeal muscles. Because of the loose areolar tissue about the esophagus, rapid dissemination of infection takes place after perforation. The speaker presented a series of 26 cases of acute suppurative mediastinitis, 23 of which were due to esophageal perforations. Twenty-one operations were performed, with 4 deaths. Of the 5 patients not operated upon, 4 died. The diagnosis can be made by the history of the patient's having swallowed a foreign body or of having had an esophagoscopy followed by pain, subcutaneous emphysema, x-ray evidence of a foreign body or of emphysema, and by direct examination of the esophagus by esophagoscopy. The speaker recommended immediate surgical treatment by making an incision along the medial aspect of the sternocleidomastoid muscle, dissecting into the superior mediastinum and inserting several Dakin's tubes. If the posterior mediastinum is involved, it is necessary to remove segments of the upper ribs posteriorly. The patient is then fed through a nasal tube and Dakin's solution is used in the wound. He showed many clinical cases, roentgenograms, and slides of the wound demonstrated by lipiodol injections. He made a plea for early operation in mediastinitis and said that the condition is curable.

Simon Jesberg, Los Angeles, Calif., stated that very few foreign bodies rupture through the esophagus spontaneously, but that a perforation usually follows instrumentation. He condemned blind instrumentation of the esophagus and urged early drainage of the mediastinum, if possible, as soon as the diagnosis is made and before sepsis is present.

Claude Frank Dixon, Rochester, Minn.: **Management of Intestinal Fistulas.**—Dr. Dixon reported ninety cases of intestinal fistula and felt that the incidence had increased in the last few years due to cases of regional ileitis, appendicitis, and other causes. Intestinal fistulas may be associated with pelvic inflammatory disease, diverticulitis, tuberculosis, actinomycosis, and nonspecific granuloma. Apparently, technical difficulties during an operation have been responsible for some fistulas.

If the fistula arises from the small bowel, conservative treatment is often the best plan. One should always determine the location and nature of the fistula before any operative procedure is carried out. It is very important to prevent dehydration of the patient and prevent or treat excoriation of the skin about the fistulous tract. Spontaneous closure may result if conservative measures are used, but if there is obstruction distally, surgical treatment is necessary, usually a resection of the bowel. For severe excoriations of the abdominal wall, tannic acid, 5 to 10 per cent solution, has been used as a spray, with good results in many cases. The author

also makes use of a Koalin-protected pasteboard trough which is placed about the fistulous opening; the skin is covered with saline solution and water and continuous suction into the trough keeps the intestinal content off the skin. He advocated enterostomy proximal to the closure of the fistula and has utilized intraperitoneal vaccine for the prevention of peritonitis.

Gunther W. Nagel, San Francisco, Calif., stated that previous surgical operations have been a prominent cause of intestinal fistula and that the surgeon should reduce the number of these. He advocated, in addition to the foregoing regime, fresh air and sunshine.

Alton Ochsner, New Orleans, La., stressed the importance of determining the etiology of the fistula in every instance and, in addition to barium by mouth or rectum, he also recommended the introduction of lipiodol into the fistulous tract; occasionally after its injection, he has noted a cure of the fistula. For protection of the skin about the fistulous tract he has utilized bronzing powder which is made up of aluminum paint and cold cream mixtures.

Frederick A. Coller, Ann Arbor, Mich.: **Surgical Aspects of Hypoglycemia Associated With Liver Damage.**—Dr. Coller presented three cases of gall-bladder disease associated with hypoglycemia, in which hunger, coma, loss of consciousness, or symptoms of disease of the nervous system were relieved following cholecystectomy. He stated that adenomas of the pancreas, adrenal glands, or pituitary body, and disease of the liver have been reported as causes of hypoglycemia. If the hypoglycemia is not due to tumor of the pancreas, he feels that the liver should be considered as a possible cause.

The first patient was a man subject to attacks of coma, with a low blood sugar level and a glucose tolerance curve which remained elevated. This curve is similar to a diabetic curve, except that the initial level is low. At operation, his pancreas was found to be normal, without evidence of adenoma. There was an early cirrhosis of the liver and a contracted diseased gall bladder. The gall bladder was removed. The patient's glucose tolerance curve returned to normal and he had no further attacks of coma.

The second case was that of a patient who complained of hunger, polydipsia, polyuria, tremors, and weakness before meals. He had a definitely altered glucose tolerance curve, and at operation a diseased gall bladder with stones and an early interlobular hepatitis were found. Cholecystectomy was done and the patient has had no further attacks of weakness or tremor since then.

The third case was that of a patient who was subject to attacks of unconsciousness. At the end of a glucose tolerance test, he lost consciousness and had a lowered blood sugar. At operation the pancreas was negative. A diseased gall bladder with a stone was removed and the patient improved clinically thereafter and his hypoglycemia was not so marked as previously.

In these three cases tests of function showed definite damage to the liver, and the biopsies of the liver revealed cirrhosis or inflammatory infiltration.

Dr. Coller stressed the importance of the administration of glucose in operations on the gall bladder. In each of these three cases the patient's glucose tolerance curve varied from the normal, the pancreas was normal, and the carbohydrates were oxidized normally in all cases, suggesting that the pancreas did not play a part, and all the symptoms were modified by cholecystectomy.

Emile Holman, San Francisco, Calif., stressed the importance of the administration of glucose before gall-bladder operations. It is his practice to give 100 c.c.

of 10 per cent solution of glucose immediately before the operation to replenish the liver glycogen because of the omission of breakfast. He felt that the good results following surgery in Dr. Coller's cases were due to better regulation of food and glucose intake rather than to cholecystectomy. He cited similar cases in which the results were good without cholecystectomy.

Frank L. Allan, Boston, Mass., stated that the patients must have a low blood sugar during their paroxysms of symptoms in order to ascribe their symptoms as being caused by hypoglycemia. In Dr. Coller's third case the blood sugar was noted to be low at the end of the glucose tolerance test, which occasionally occurs in normal persons. He did not feel that the cause of hypoglycemia can be explained by such a simple test as that of glucose tolerance when there are so many factors which affect the level of sugar in the blood stream. Damage to the liver gave the discussant reason for urging early operation for gallstones before injury to the liver occurs.

Theodore L. Althausen, San Francisco, Calif., cited animal experiments showing, both in animals with normal livers and in those with livers diseased by the injection of phosphorus, the protective action of glucose on the liver, and the delayed glucose tolerance curve in the animals with diseased livers. One may obtain various types of glucose tolerance curves in disease of the liver, depending on the degree of damage. He advocated the glucose tolerance test supplemented by insulin in order to accentuate differences. He stated that, in his experience, the administration of glucose in large amounts had been a factor in the reduction of postoperative mortality from cholecystectomy.

Amos R. Koontz, Baltimore, Md.: **Does Ether Narcosis Protect From Anaphylactic Shock?**—Dr. Koontz stated that there is a general impression among surgeons that ether narcosis protects the patient from anaphylactic shock, so that tetanus antitoxin is often administered under anesthesia without using the usual precaution to determine the patient's sensitivity to horse serum before the injection. A large number of guinea pigs were sensitized with various types of foreign protein. After their period of sensitization, of those which were reinjected with the same foreign protein without anesthesia, 47.8 per cent died. Of those which were injected under ether anesthesia, 18 per cent died. This definitely suggests that anaphylactic reaction is less likely to occur under ether anesthesia, but there still is danger. Ether, therefore, inhibits anaphylactic shock, but because such shock does occur in some cases, the usual precaution of cutaneous or ophthalmic tests should be used to determine whether or not the patient is sensitive to the foreign protein.

Franklin I. Harris, San Francisco, Calif., discussed the paper from a clinical standpoint. He referred to the observations of Dew, who noted that anaphylactic reactions almost never occurred when hydatid cysts were opened under ether anesthesia, but anaphylactic reaction might occur if local anesthesia, or none, was used. He also noted that reactions never occur under narcosis if blood, glucose, or saline solutions are administered intravenously, stating that there is a definite protection by the anesthetization. Nevertheless, this protection may not be complete so that it is necessary to test the patient for cutaneous reaction before he is anesthetized.